



PHD

The exploration of rhodium-catalysed additions of organoboranes

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THE EXPLORATION OF RHODIUM-CATALYSED ADDITIONS OF ORGANOBORANES

Submitted by Kelly Jane Harris
for the degree of PhD
of the University of Bath
2004

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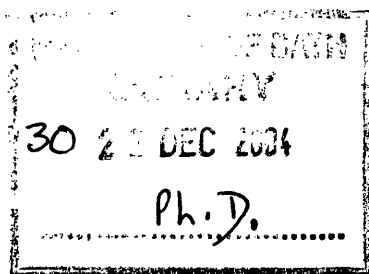
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SYNOPSIS

Transition metal catalysed carbon-carbon bond forming reactions are central to the synthesis of many biologically interesting molecules. Amongst the many catalytic transformations the rhodium-catalysed addition reaction has seen a recent rise in popularity; this is due to the broad applicability of the chemistry to a range of substrates with a variety of functional groups. Many substrates are able to perform both 1,4- and 1,2-additions and the mechanism by which this occurs has been well documented. However there are still many substrates available by which to extend the scope of these reactions and questions as to what effects these new substrates may have on the current ideas of the mechanism and the accepted origin of enantioselectivity.

This thesis describes the exploration of rhodium catalysed addition reactions with organoboranes encompassing a synthesis of simple arylketones and the 1,4-addition to dialkyl itaconic esters.

The first chapter reviews rhodium catalysed additions through the application of a range of organoboranes. This includes a detailed discussion on the accepted mechanism and highlights some of the more unusual outcomes as well as the more established 1,4- and 1,2-addition products.

Chapter two describes the discovery of a new methodology for the synthesis of simple ketones. This method successfully exploits the rhodium/boron transmetallation process to achieve a highly versatile procedure which is not hindered by the characteristic functional groups restrictions of Friedel Crafts reactions.

The third chapter establishes the 1,4-addition of organoboronic acids to dimethyl succinates. This is primarily achieved, racemically, in water and then, through the exploration of many parameters, asymmetrically in organic solvents. This study highlights the fact that when dealing with 1,1-disubstituted activated alkenes it is more difficult to produce enantioselective results as the chirality is determined in the protonation step and not during insertion.

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And finally, my Ali. Who has cheered me on from the side lines and picked me up when I fell down. I have put you through so much in these last few months and you’ve loved me all the same. I could not have asked for more in a husband, nor could I love you more.

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ABBREVIATIONS

Å	angstrom(s)
Ac	acetyl
Acac	acetylacetate
aq	aqueous
Ar	aryl
Atm.	Atmospheres
Bn	benzyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
B _{mim} PF ₆	1-butyl-3-methylimidazolium hexafluorophosphate
Bppfa	1',2-bis(diphenylphosphino)-1-(N,N-dimethylaminoethyl) ferrocene
Bu	normal (primary) butyl
^t Bu	<i>tert</i> -butyl
Bz	benzoyl
°C	degrees Celsius
calcd	calculated
cat.	catalyst
Cbz	benzyloxycarbonyl
cm ⁻¹	wavenumber(s)
COD	1,5-cyclooctadiene
COE	cyclooctene
CuTC	copper(I) thiophene-2-carboxylate
Cy	cyclohexyl
δ	chemical shift in parts per million downfield from tetramethylsilane

d	day(s); doublet (spectral)
dba	dibenzylideneacetone
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCM	dichloromethane
°	degrees (angle)
DIOP	2,3- <i>O</i> -Iosproylidene -2,3-dihydroxy-1,4bis(diphenylphosphino)butane
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
dmba	<i>N,N</i> -dimethylbenzylamine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
EDCI	<i>N</i> -(3-dimethylaminopropyl)- <i>N</i> -ethylcarbodiimide hydrochloride
EI	electron impact (in mass spectrometry)
Et	ethyl
equiv.	equivalent(s)
FAB	fast atom bombardment (in mass spectrometry)
g	gram(s)
h	hour(s)
H-BCat	catecholborane

HMPT	hexamethylphosphorustriamide
HOBT	1-hydroxybenzotriazole
HPLC	high-performance mass spectrometry
Hz	hertz
IR	infrared
<i>J</i>	coupling constant (in NMR spectrometry)
L	litre(s)
ν	wavenumber(s)
LHMDS	lithium hexamethyldisilazane, lithium bis(trimethylsilyl)-amide
lit.	literature
μ	micro
m	milli; multiplet (spectral)
M	molar (moles per liter); mega
M^+	parent molecular ion (in mass spectrometry)
Me	methyl
MeO-MOP	2-(diphenylphosphino)-2'-methoxy-1,1'-Binaphthyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
MVK	methyl vinyl ketone
<i>m/z</i>	mass-to-charge ratio (in mass spectrometry)

NMR	nuclear magnetic resonance
Ph	phenyl
PMB	<i>para</i> -methoxybenzyl
PPF	diphenylphosphino ferrocene
ppm	part(s) per million
Pr	propyl
q	quartet (spectral)
R_f	retension factor (in chromatography)
rt	room temperature
s	singlet (spectral)
SDS	sodium dodecyl sulphate
t	triplet (spectral)
TEBA	benzyltriethylammonium chloride
TFA	trifluoroacetic acid
TFP	Tris(<i>o</i> -furyl)phosphane
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMS	trimethylsilyl; tetramethylsilane
TPPDS	disulfonated triphenylphosphine, disodium salt
t_R	retention time (in chromatography)
Ts	<i>p</i> -toluenesulfonyl (tosyl)

CHAPTER ONE:
***Literature Review of Rhodium-Catalysed Additions
of Organoboranes***

1 LITERATURE REVIEW OF RHODIUM-CATALYSED ADDITIONS OF ORGANOBORANES

1.1 INTRODUCTION

Carbon-carbon (C-C) bond forming reactions are of the utmost importance to the organic chemists. This is reflected by the continued high level of research and growing number of methods available to perform this operation. Transition metals in particular are increasingly being employed as catalysts for these reactions with palladium principally being utilised. Palladium catalysts can perform a whole range of versatile reactions including Kumada-Corriu,¹ Mirozoki-Heck,² Stille,³ and Suzuki-Miyaura⁴ coupling reactions which permit the cross-coupling of a range of substrates.

One of the most important carbon-carbon bond forming reactions is the conjugate addition to alkenes. The use of metal catalysts in combination with organometallic reagents has been particularly effective producing products in high yield and enantioselectivity. Metals used to catalyse these reactions include copper,⁵ rhodium,^{6,7} zinc, and palladiums while the organometallics applied include Grignard, organozinc and organolithium reagents.

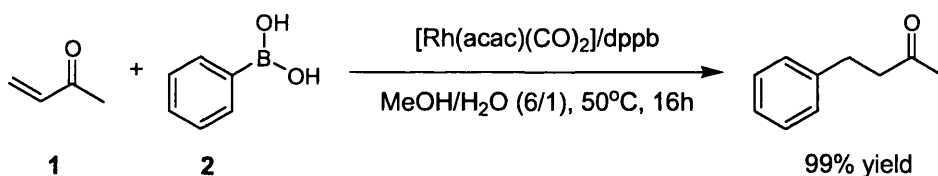
Recently rhodium, in combination with organoboranes, has seen increasing application in this area with the catalytic systems possessing new and complementary reactivity to previously used catalyst systems. Rhodium has the added advantage over other metals, from an environmental perspective, as water can be used as a co-solvent and even the sole solvent in number of reactions. In addition the use of organoboranes is advantageous due to their low toxicity, high tolerance for functional groups and relatively high level of stability in air.

This chapter will provide an overview of rhodium-catalysed carbon-carbon bond forming reactions using organoboranes.

1.2 1,4-CONJUGATE ADDITION

1.2.1 Additions To Enones

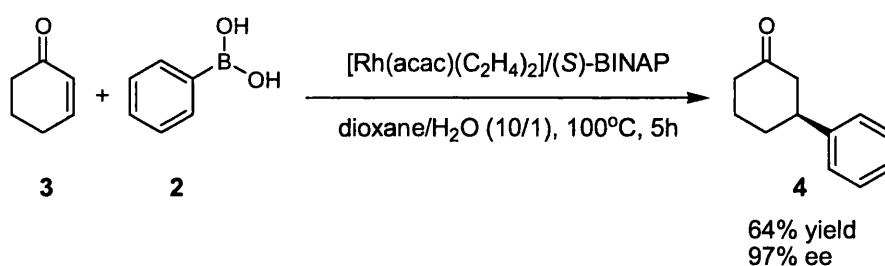
Miyaura and co workers first published the rhodium-catalysed 1,4-addition of aryl- and alkenyl-boronic acids to enones in 1997.⁸ This initial report obtained the addition products in high yields with the combination of $[\text{Rh}(\text{acac})(\text{CO})_2]$ and dppb as the catalyst in methanol/ H_2O (6/1) at 50°C . The quantity of water present is a significant factor in achieving a high yield since too much water leads to the hydrolysis of the boronic acid, however, no reaction occurs in the absence of water. A range of bis(phosphine) ligands were examined, the results of which indicated that as the P-Rh-P angle (bite angle) increased the rate of reaction also increased. This led to the series $\text{dppb} > \text{dppp} > \text{TFP} > \text{dppe}$, PPh_3 & AsPh_3 . This effect is more pronounced when using the less reactive 2-octen-4-one as the substrate. Methyl vinyl ketone **1** on the other hand, gave excellent yields for all ligands (Scheme 1). No appreciable difference was noted for electron-withdrawing or donating groups on the boronic acid, although sterically hindered boronic acids such as 2-methoxyphenylboronic acid required extended reaction times and two equivalents of boronic acids to achieve a significant yield.



Scheme 1

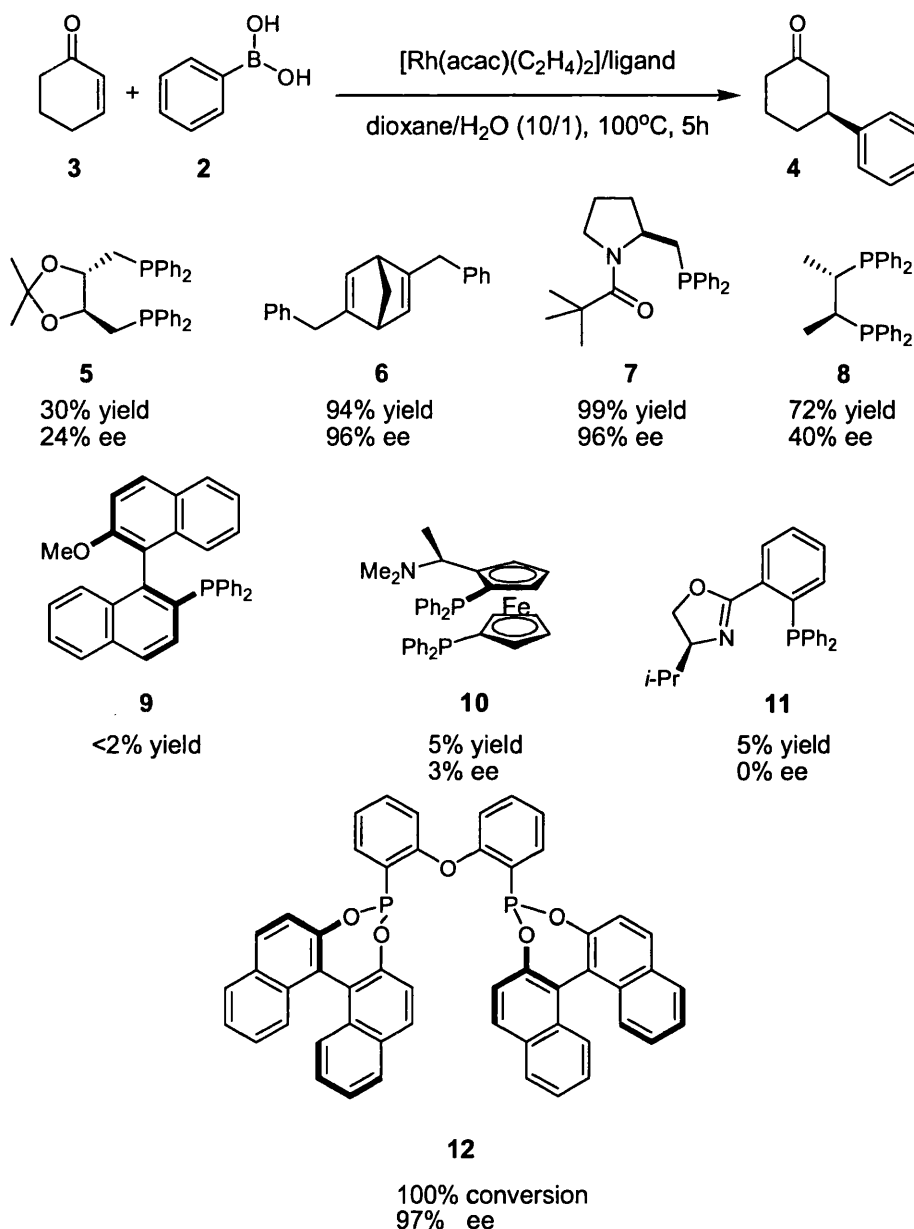
These conditions were then modified to include the asymmetric 1,4 addition of boronic acids.⁹ Most significant was the change in catalyst to $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$, which formed the chiral rhodium-BINAP complex instantly when stirred with the chiral phosphine ligand. The co-ordination of BINAP with $[\text{Rh}(\text{acac})(\text{CO})_2]$ was much slower and led to a mixture of catalysts being formed, the components of

which were not investigated further. For the addition to cyclohexenone an increase in temperature (100°C) and a change in solvent (dioxane/water (10/1)) led to a 64% yield of (S)-3-phenylcyclohexanone **2** with a 97% enantioselectivity after only 5 hours (Scheme 2). The elevated temperature led to an increased hydrolysis of phenyl boronic acid thus between 1.4 and 5 equivalents of boronic acid were required to achieve a reasonable yield. A wide variety of electron-deficient and electron-rich boronic acids were tolerated with linear as well as cyclic enones proving successful.



Scheme 2

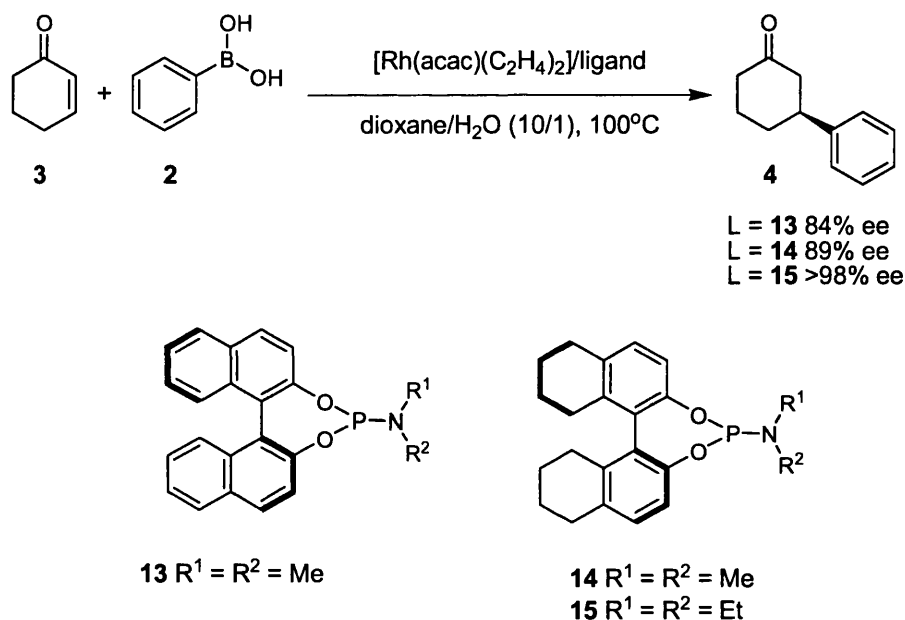
Although BINAP was used very successful as the first chiral ligand to be applied to the 1,4-addition to cyclohexenone, a vast range of ligands have since been employed with varying success (Scheme 3). High yields are obtained for chelating bisphosphine ligands such as DIOP **5** and Chiraphos **8** but these do not compete enantioselectively.¹⁰ Monodentate phosphines (MeO-MOP) **9**, and phosphines containing an oxazoline (ip-phox) **11** or an amino group (bppfa) **10** all performed disappointingly with low yields and ee's. Amidomonophosphine **7**, a ligand derived from L-proline, gave comparable enantioselectivity through a hemi-labile mechanism. The chelating ability of this ligand proved crucial as other derivatives that had poorer chelating ability resulted in a lower ee.¹¹ Using identical conditions Reetz proposed 1,1'-binaphthol-based diphosphonites **12** which are strongly dependent on the achiral backbone for their selectivity.¹² These ligands performed well giving high ees from a much lower catalyst loading. Chelating dienes such as the norbornadiene based ligand **6** also performed extremely well with 94% yield and 96% ee.



Scheme 3

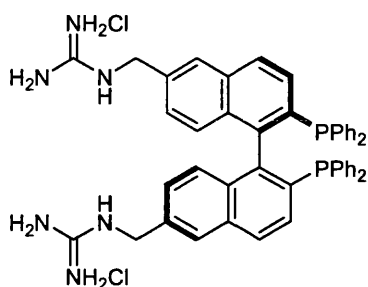
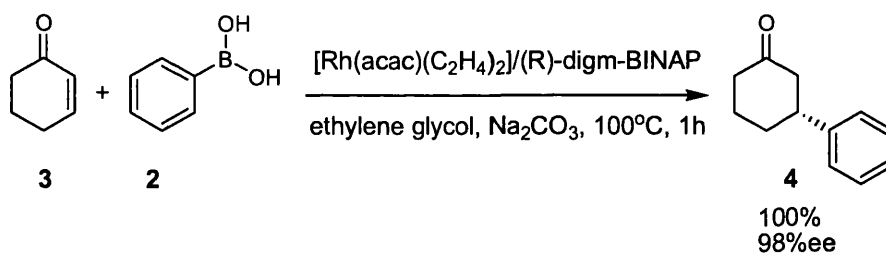
More recently, Feringa and co-workers have shown phosphoramidite **13** (MonoPhos) (Scheme 4) to be successful in the addition of phenylboronic acid **2** to cyclohexenone **3** affording the desired product **4** with 100% conversion and 84% ee when used in combination with $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$ in dioxane/water at 100°C .¹³ Miyaura also demonstrated that at 50°C the same high selectivity and reactivity can be obtained, if potassium hydroxide is added to the reaction mixture, producing 3-

phenylcyclohexenone **3** in 95% yield and 98% enantiopurity.¹⁴ Feringa expanded on this by synthesising and investigating a range of phosphoramidites.¹⁵ Phosphoramidite **15** proved most successful with catalyst loading being able to be reduced to only 0.05 mol% with no loss in yield or enantioselectivity. When compared directly to BINAP it was shown that phosphoramidite **15** reached full conversion after 10 minutes, whereas BINAP had only reached 20% conversion. Contrary to standard observations enantioselectivity was not temperature dependent and high selectivity (>94%ee) was seen for temperatures in the range of 45°C-140°C.



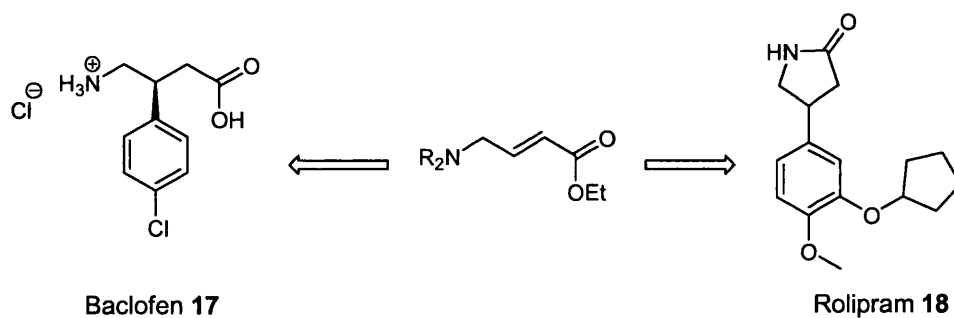
Scheme 4

The water soluble ligand, (*R*)-digm-BINAP **16**, encompasses a BINAP skeleton as a basic structure and contains two guanidinium salts on the binaphthyl, has been utilised by Michlet and Genet in the rhodium-catalysed 1,4-addition.¹⁶ Although this catalyst system fails when water is used as the only solvent, phenylation of 2-cyclohexenone **3** efficiently occurs in ethylene glycol in the presence of sodium carbonate with catalyst loadings as low as 0.005% and proceeds with high yields and enantioselectivity (Scheme 5).

(R)-Digm-BINAP **16**

Scheme 5

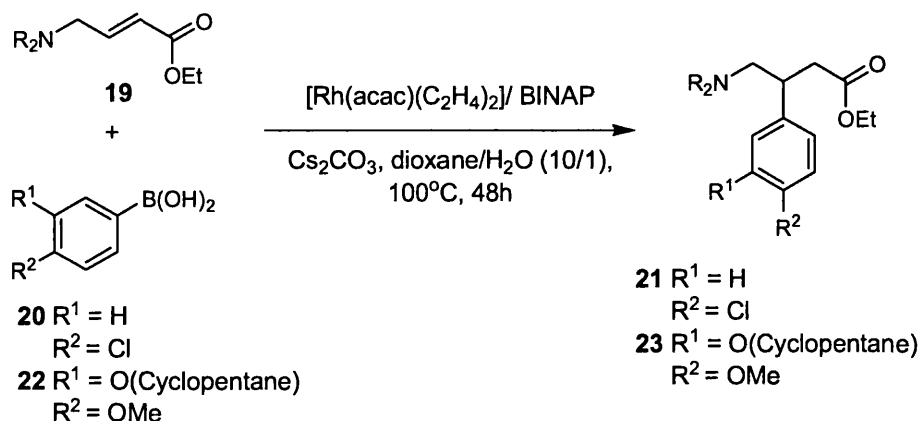
Rhodium-catalysed conjugate additions have been applied to natural product synthesis such as (-)-(*R*)-Baclofen ((*R*)-4-amino-3-(4-chlorophenyl)-butyric acid) **17** and other GABA analogues such as (-)-(*R*)-Rolipram (4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-one) **18** (Scheme 6).



Scheme 6

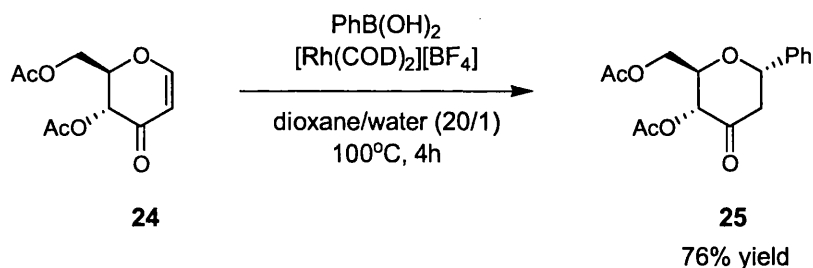
Helmchen^{17,18} demonstrated that when α,β-unsaturated γ-aminobutyric acid ester **19** is treated with 4-chlorophenylboronic acid **20** in the presence of $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]/(\text{S})\text{-BINAP}$ with cesium carbonate as base in dioxane/water (10/1) at 100°C protected γ-aminobutyric acid **21** is produced in 96% yield and 87% ee

(Scheme 7). This product **21** was then further reacted to afford Baclofen **17** in just two more steps. Similarly, Rolipram **18** is synthesised through the use of boronic acid **22**. In fact a number of Boronic acids proved successful in providing an array of derivatives of both these GABA analogues.



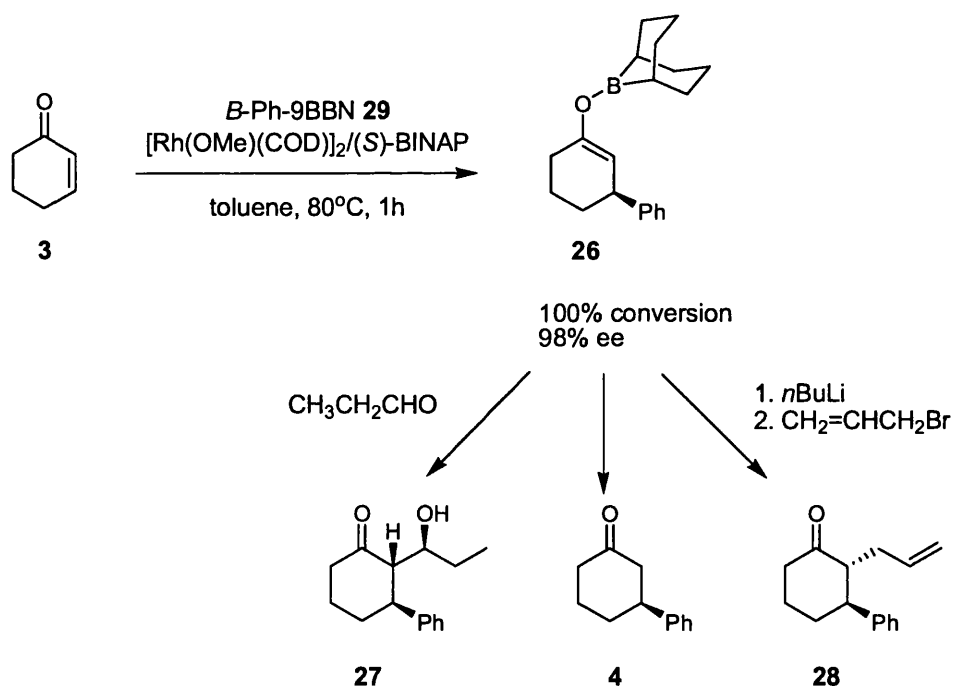
Scheme 7

C-Glycosides possess potent antibacterial, antiviral and antitumor activities. Maddaford demonstrated that they could be efficiently prepared through rhodium-catalysed 1,4-addition of arylboronic acids to enones derived from glycols (Scheme 8).¹⁹ This reaction proved to be stereoselective for the α -anomer and is highly dependent on the nature of the rhodium catalyst. For example $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$ in the presence of phosphine ligands failed to yield any of the desired 1,4-addition product. However, when $[\text{Rh}(\text{COD})_2][\text{BF}_4]$ is heated to 100°C with phenylboronic acid and **24** in dioxane/water (20/1) 76% of **25** was obtained after 4 hours. ^1H and ^{13}C NMR revealed the presence of a single anomer for all products, which were assigned the α -configuration by comparison with known products. A variety of boronic acids were effectively coupled and identified in this fashion in moderate to high yields.



Scheme 8

In all of the previous examples, the product has been obtained via hydrolysis of the boron intermediate. However, Hayashi proposed that the boron enolate intermediate **26** would be a more useful product which could be hydrolysed or manipulated as desired to give a range of products, examples of which are shown in Scheme 9.

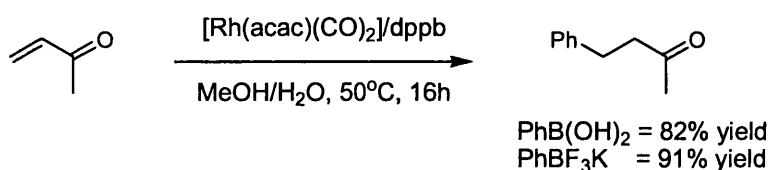


Scheme 9

2-Cyclohexenone **3** reacts with 1.1 equivalents of *B*-Ph-9BBN **29** in the presence of 3mol% $[\text{Rh(OMe)(COD)}_2]/(S)\text{-BINAP}$ in anhydrous toluene at 80°C for 1 hour to give product **26** in high yield and 98% ee.

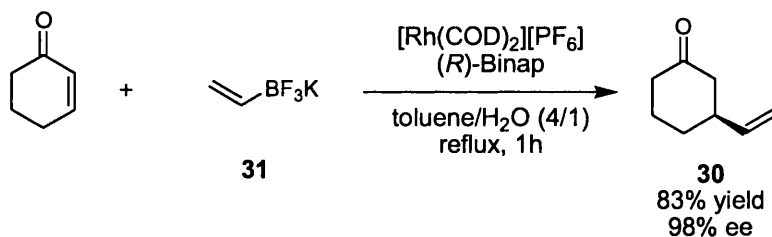
Additions of Potassium Trifluoroborates

Potassium trifluoroborates are known to be a more stable alternative to boronic acids, making them a favourable choice for addition reactions in aqueous solutions. Batey *et al.* demonstrating their use under Miyuuri's original conditions of $[\text{Rh}(\text{acac})(\text{CO})_2]$ with dppb in methanol/water at 50°C (Scheme 10).²⁰ This proved successful and the enhanced stability and increased reactivity led to a broader range of aryl and alkenyl groups being successfully coupled under milder conditions.



Scheme 10

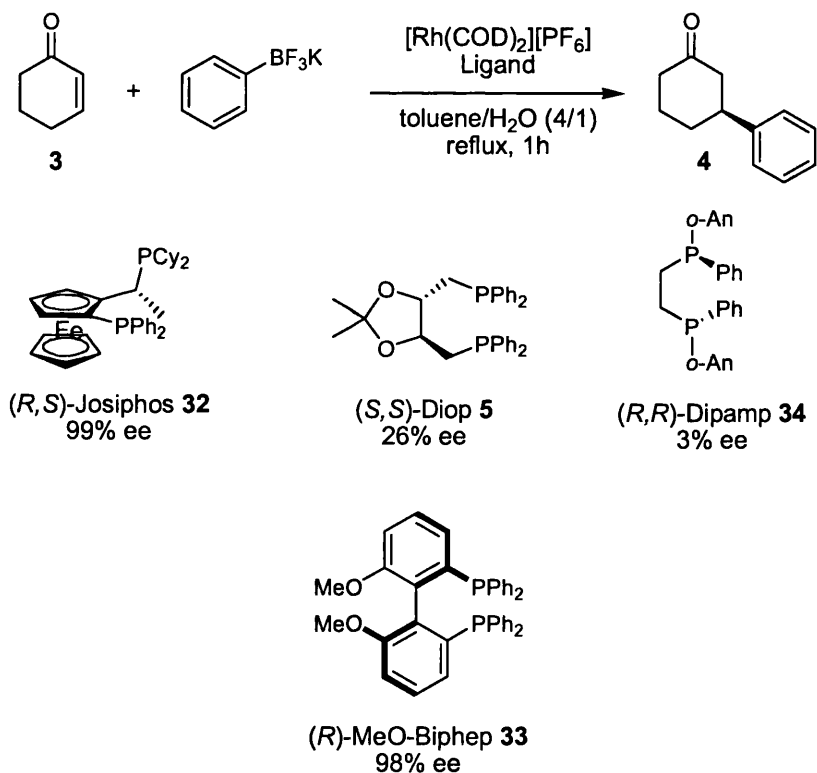
Genet found that cationic rhodium catalyst $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ performed better in combination with trifluoroborates. In the presence of a rhodium catalyst generated from $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ and (*R*)-BINAP in toluene/water (4/1), the addition of vinyl trifluoroborate to 2-cyclohexenone proceeded at $105\text{--}110^\circ\text{C}$ to give a high yield of vinylation product **30** with 98% ee.



Scheme 11

Interestingly, the reactions of potassium organotrifluoroborates have some characteristic features that differ from those of the organoboronic acids. Such as the fact that their reactions display a low reactivity when catalysed by complexes generated from neutral rhodium sources such as $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$, and the enantioselectivity obtained is highly dependent on the bulk solvent employed. The

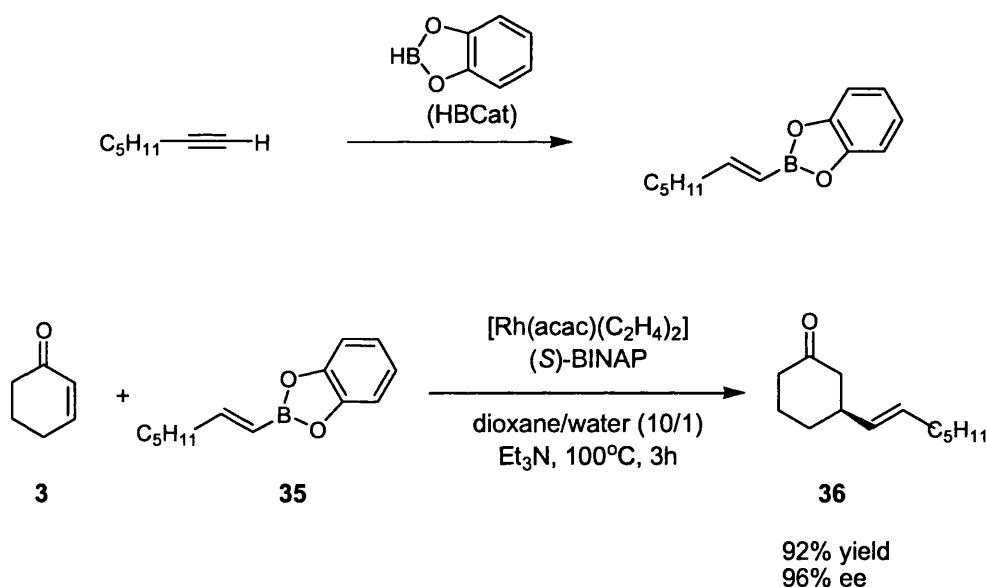
use of toluene as co-solvent and an excess amount of water was found to be important for a high enantioselectivity. It is remarkable that an unsubstituted vinyl group can be introduced in a high yield by use of vinyl trifluoroborate **31**; the corresponding vinyl boronic acid cannot be used due to its instability under the reaction conditions (Scheme 11). Genet and co-workers, have also examined several other chiral bisphosphines for the reaction of phenyltrifluoroborate with cyclohexenone (Scheme 12). The highest enantioselectivities were observed with (*R*)-(*S*)-Josiphos **32** (99%ee) and (*R*)-MeO-Biphep **33** (98%ee), whilst the lowest were obtained with the less bulky (*R,R*)-DIOP **5** (26%ee) and (*R,R*)-Dipamp **34** (3%ee).



Scheme 12

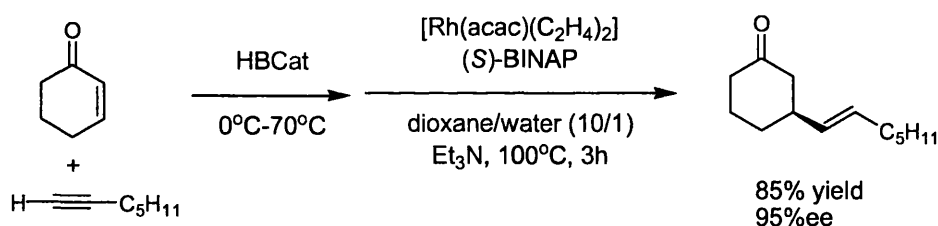
1.2.2 One-Pot Reactions: Organoborane Formation and 1,4-additions

Alkenylcatecholboranes are obtained by the hydroboration of alkynes with catecholborane (Scheme 13). Hayashi demonstrated their use in asymmetric 1,4-addition to cyclohexenone.²¹ In the presence of 3 mol% $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]/\text{BINAP}$ and triethylamine in dioxane/ H_2O (10/1) at 100°C , the reaction of (*E*)-1-heptenylborane **35** with cyclohexenone **3** produced 92% of the addition product **36** in 96% enantiomeric purity. The addition of base is required to neutralise the acidic conditions formed by the hydrolysis of the alkenylcatecholborane, in the absence of base the yield was only 27%.



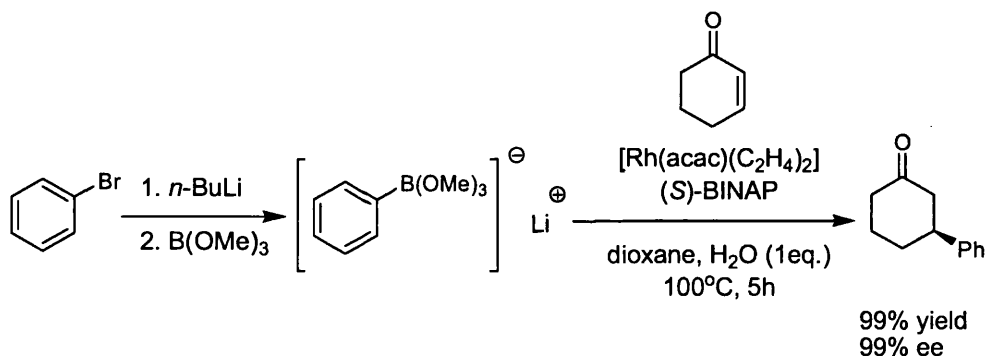
Scheme 13

This reaction was proven to be successful in a one-pot process, with the *in situ* formation of the boron intermediate. These conditions were then applied to a variety of alkynes and enones using five equivalents of borane and two equivalents of triethylamine resulting in high yields and enantioselectivities (Scheme 14).



Scheme 14

Another one-pot synthesis demonstrated by Hayashi uses lithium trimethylborates, readily generated from treatment of aryl bromides with butyl lithium and trimethoxyborane (Scheme 15).²² Although no additional base was required the amount of water present greatly affected the yield, however the enantioselectivity remained undisturbed. Optimum yields were obtained with one equivalent of water to cyclohexenone. These lithium trimethylborates proved superior to boronic acids in both yield and enantioselectivity over a range of substrates.



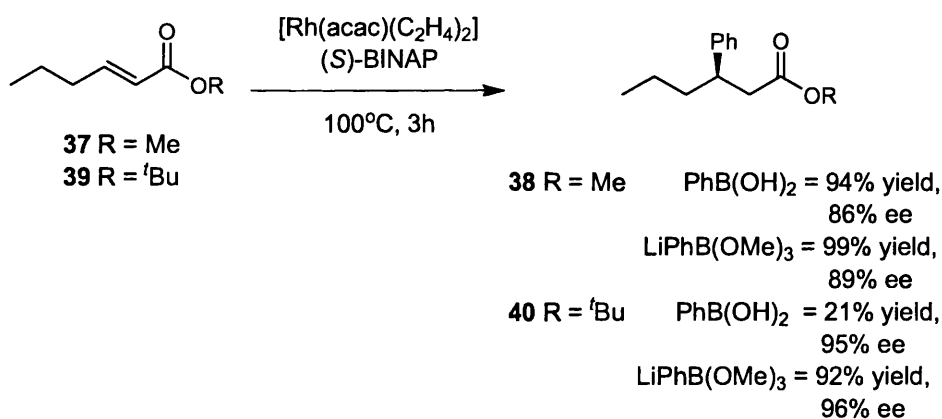
Scheme 15

The main advantage of both of these routes is that there is no need to isolate the boron reagent formed.

1.2.3 Additions to α,β -Unsaturated Esters

α,β -Unsaturated esters have proven to be less reactive than their ketone counterparts requiring higher temperatures and are more sensitive to steric bulk when applied to

rhodium-catalysed 1,4-additions. For example, (*E*)-methyl hex-2-enoate **37** reacted with phenylboronic acid in the presence of $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]/\text{BINAP}$ in dioxane/water (10/1) at 100°C to generate the addition product **38** in 94% yield and 86% ee (Scheme 16).²³ However, when the methyl ester is replaced by a *t*Bu the yield drops dramatically to 21%. This is attributed to the phenylboronic acid being consumed by hydrolysis before the reaction is complete. The use of lithium organoborates not only improves the yield, but also increases the enantioselectivity. For example, (*E*)-*t*-butyl hex-2-enoate **39** reacts with lithium phenylborate (generated *in situ* from phenyllithium and trimethylborate) in the presence of $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]/\text{BINAP}$ in dioxane with one equivalent of water (to lithium phenylborate) at 100°C to produce **40** in 92% yield and 96% enantiomeric excess.



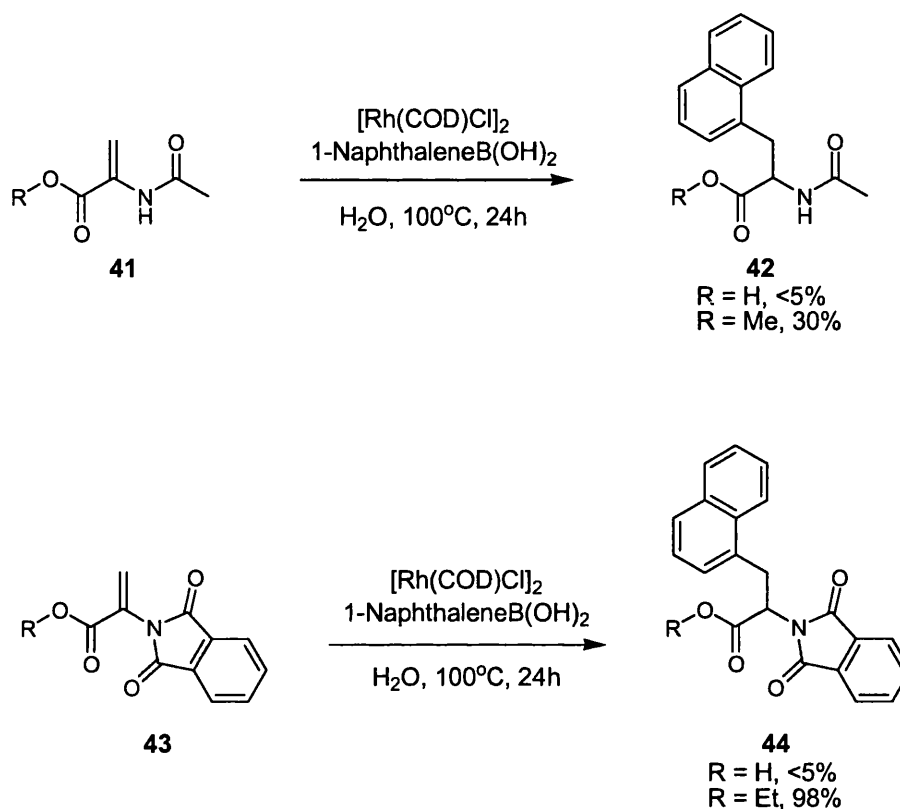
Scheme 16

It is thought that the addition of one equivalent of water is necessary to generate the reactive $\text{Li}[\text{PhB}(\text{OMe})_2(\text{OH})]$ species or $\text{PhB}(\text{OMe})(\text{OLi})$ from $\text{Li}[\text{PhB}(\text{OMe})_3]$. This is supported by that fact that $\text{PhB}(\text{OMe})_2$ does not react with cyclohexenone in the absence of an additive, but upon addition of lithium hydroxide the reaction is driven to completion.²²

Interestingly, cyclic enones afford higher yields when boronic acids are used instead of lithium organoborates.^{23,24}

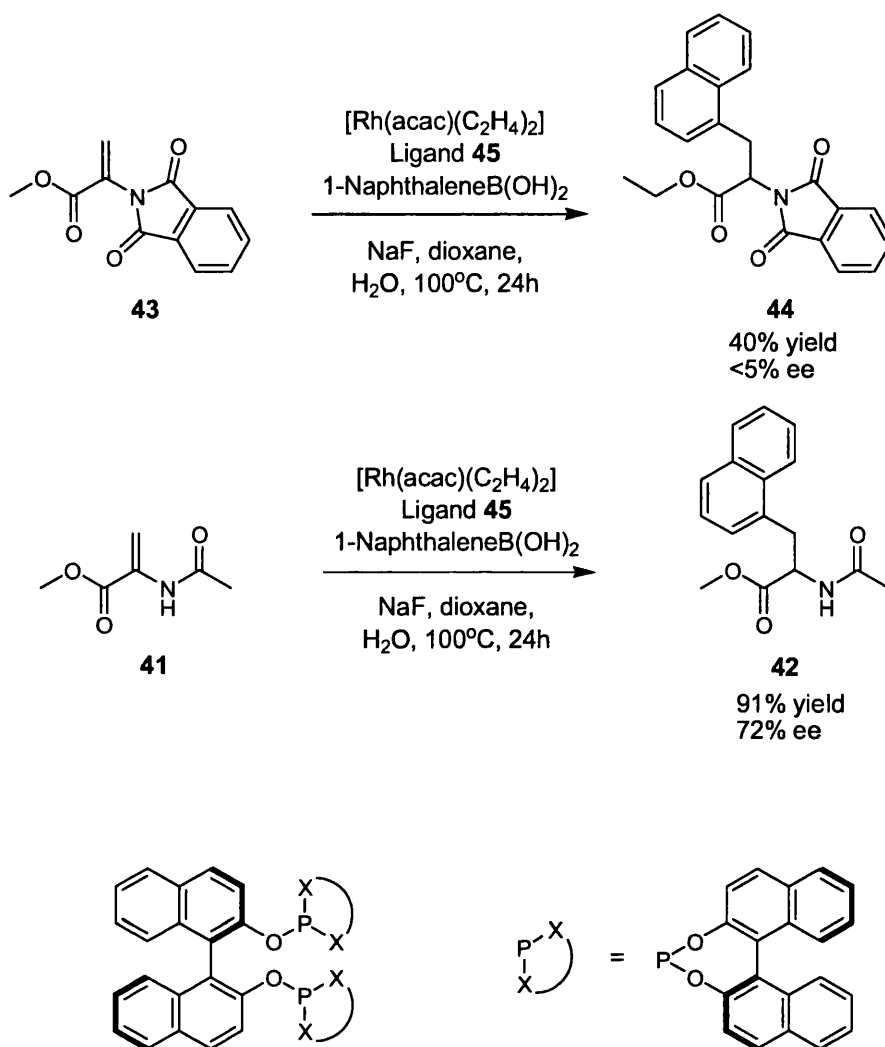
1.2.4 Additions To Dehydroamino Acid Derivatives

α -Amino acids are important building blocks in drug discovery the production of a wide variety of substituted phenylalanine-type α -amino acids have recently been synthesised by Frost and Chapman. They revealed an efficient rhodium-catalysed conjugate addition of boronic acids to α,β -dehydroamino acid derivatives using only water as a solvent (Scheme 17).²⁵ Initial studies with dehydroalanine derivative **41**, in water gave disappointing results with a maximum 30% yield obtained with 1-naphthaleneboronic acid and $[\text{Rh}(\text{COD})\text{Cl}]_2$, this low yield is proposed to be as a result of the intolerance of the acrylate to the aqueous conditions. The introduction of the phthalimide nitrogen protecting group and esterification of the free acid group, resulted in a stable substrate which could undergo 1,4-addition. Ethyl α -phthalimidoacrylate **43** reacted with 1-naphthaleneboronic acid to give a 98% yield of **44** after 24 hours. Both protecting groups can then be cleaved under acidic conditions (6N HCl/AcOH, 4/1) to furnish the unnatural α -amino acid hydrochloride salts in good yields (Scheme 17).



Scheme 17

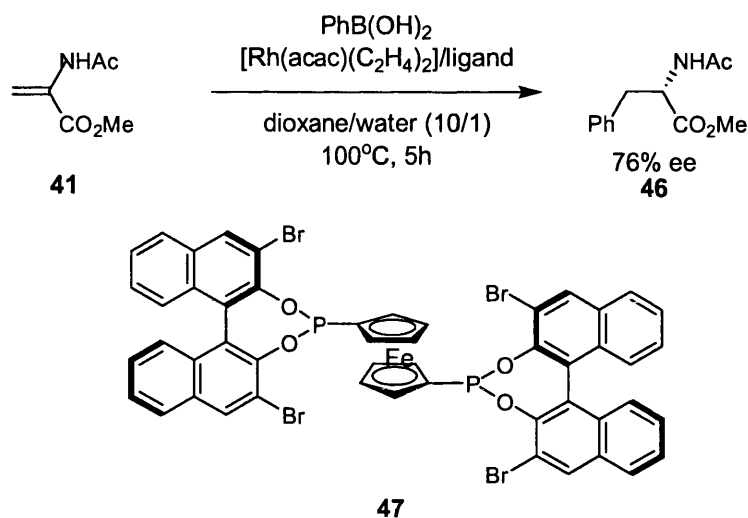
Unfortunately when the asymmetric 1,4-addition was performed on these substrates the phthalimide derivative **43** gave only a less than 5% ee (Scheme 18).²⁶ However when **41** was reacted with 1-naphthaleneboronic acid in the presence of $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$ and Pringle's, Binol derived diphosphite ligand, **45** N-acetyl-3-(1-naphthyl)alanine methyl ester **42** was produced in a 91% yield and 72% ee. It is interesting to note that the reactions could no longer be performed in water and that BINAP affords a racemic mixture of products.



Pringle's Ligand 45

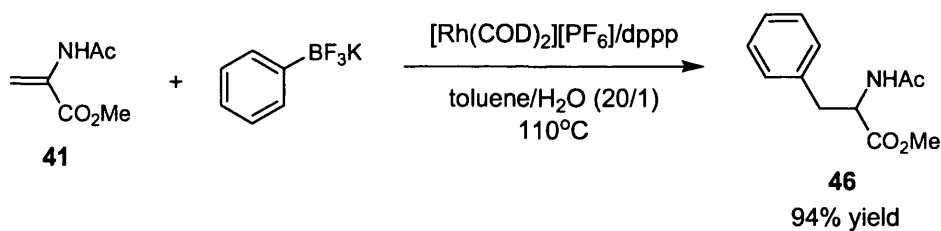
Scheme 18

Reetz also demonstrated the 1,4-addition of phenylboronic acid to α -acetamido acrylic acid ester **41**.¹² This produced phenylalanine derivative **46** in 100% conversion and 70% ee when $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)]_2$ /phosphonite **47** is used in dioxane/water (10/1) at 100°C for 5 hours. This is increased to 76% ee when three equivalents of NaF were added (Scheme 19).



Scheme 19

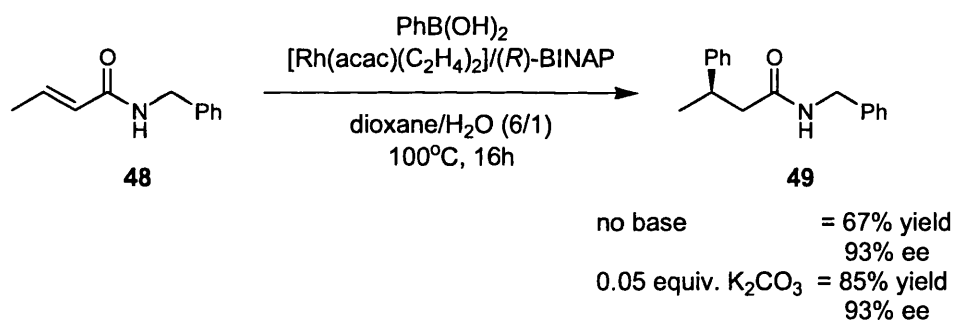
Genet *et al.* facilitated the rhodium-catalysed 1,4 addition of dehydroamino esters **41** with potassium organotrifluoroborates to produce alanine derivatives of type **46** (Scheme 20).²⁷ It was shown that potassium trifluoro(organo)borates were able to carbometallate dehydroamino esters with high efficiency in the presence of a rhodium catalyst. This reaction allowed the formation of various alanine derivatives in good to high yields ($\geq 98\%$). In contrast to similar reactions a variety of amino acid protecting groups were tolerated under the reaction conditions. A brief study of alkenyl trifluoroborates proved that while they are less successful than their aryl counterparts they still produce the addition products in reasonable yields.



Scheme 20

1.2.5 Additions To α,β -unsaturated amides

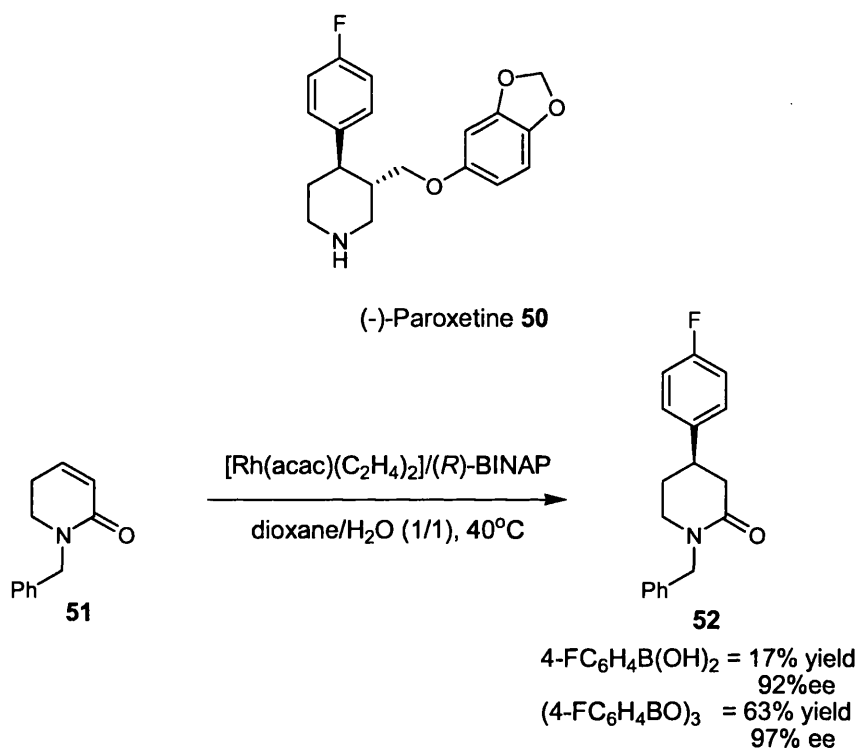
The rhodium-catalysed 1,4-addition of organoboronic acids to α,β -unsaturated amides is successfully achieved under the Miyaura conditions of $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]/\text{BINAP}$ in dioxane/water at 100°C (Scheme 17).²⁸ However, the reaction proceeds at a reduced rate, to the esters and enones, and requires one equivalent of base to obtain complete conversion. Potassium carbonate was found to be the best furnishing 85% yield and 93% ee of the addition product **49** after 16 hours. It is worthwhile to note that not only was the reaction inhibited by the addition of 5mol% HCl, but it could be restarted on addition of 15mol% K_2CO_3 . This is attributed to the formation of the more active $[\text{Rh}(\text{OH})]$ catalyst (see mechanistic studies 1.3). A variety of α,β -unsaturated amides were successfully reacted under these conditions, especially for the addition of electron deficient arylboronic acids, but *N,N*-disubstituted crotonamides were found to be unreactive.



Scheme 21

Lactam **52** is employed in the synthesis of (-)-paroxetine **50** and can be synthesised through the rhodium-catalysed 1,4 addition to its α,β -unsaturated counterpart **51** as demonstrated by Hayashi (Scheme 18).²⁹ Using the standard conditions of $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)]/(R)\text{-BINAP}$, dioxane/water (10/1) at 100°C for 16 hours gave lactam **52** in 70% yield when phenylboronic acid was used, but a disappointing 17% when 4-fluorophenylboronic acid was used; although the product was obtained with a high ee (92-3% ee) in both cases. This dramatic reduction in yield was attributed to the 4-fluorophenyl rhodium(I) intermediate being more susceptible to protonolysis,

thus destroying the aryl group before the addition can be accomplished. To inhibit this, the reaction was performed at 40°C with 4-fluorophenylboroxine and the amount of water was reduced to one equivalent to boron. Under these conditions the yield increased to 63% and the enantioselectivity also improved to 97% (Scheme 22).



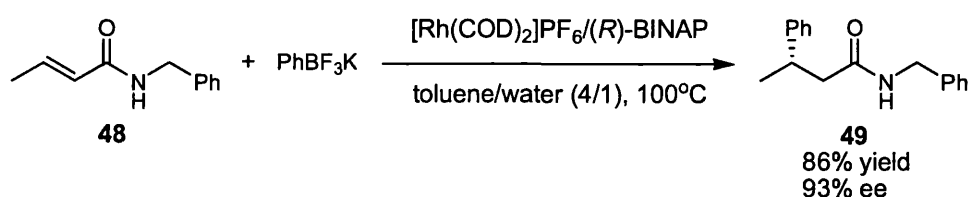
Scheme 22

Genet and co-workers continued their work with potassium trifluoroborates to the synthesis of chiral β -arylamides **49** from crotonamides **48** (Scheme 23).³⁰ It was observed that whilst the addition of base had no effect on yield, the selectivity diminished considerably from 93% ee with no additional base to 64% ee with 10% potassium fluoride. This however was not the case with boronic acids where no variation was observed. Further studies where the two boron sources were run under identical conditions and followed by GC highlighted the following points:

The potassium(trifluoro)organoborates have an induction period of 10 minutes but the reaction had reached completion after 1 hour, whereas the boronic acid reacted

immediately but reached a 62% maximum after 1 hour 40 minutes. The induction period is postulated to be due to the formation of either another more active rhodium catalyst or a different boron species.

A variety of potassium(trifluoro)organoborates were reacted under optimised conditions to afford a range of chiral β -arylamides in high yields and selectivities. Electron-withdrawing and electron-donating groups on the aryl group had no effect on yield or selectivity (Scheme 23).



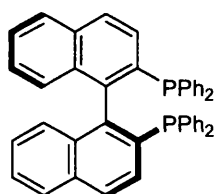
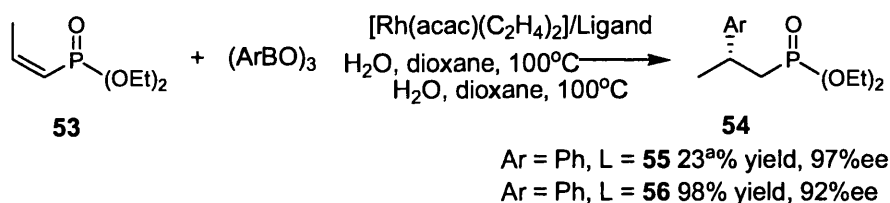
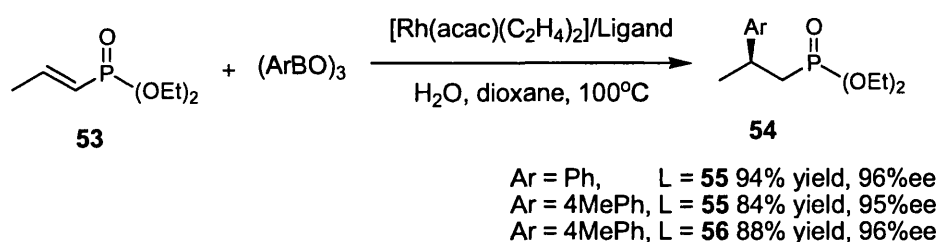
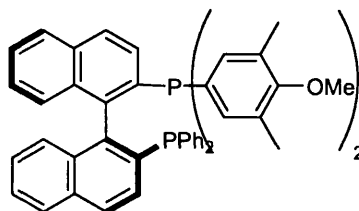
Scheme 23

1.2.6 Alkenyl Phosphonates

Optically active phosphonic acid derivatives are important compounds because of their synthetic utility as chiral building blocks as well as their potential biological activity. Despite their potential the 1,4-addition to alkenylphosphonates has remained a relatively uncharted area, this may be attributed to their low reactivity to 1,4-addition. Hayashi and co-workers found that to achieve this the standard 1,4-addition conditions needed to be modified to include the use of phenylboroxine and one equivalent of water to boron.³¹ Alkenyl phosphonate (*E*)-53 reacted with phenylboroxine in the presence of [Rh(acac)(C₂H₄)₂]/BINAP in dioxane at 100°C with the addition of one equivalent to boron of water, to yield alkyl phosphonate 54 in 94% yield and 96% ee (Scheme 24).

This reaction shows the crucial part that water has to play, as without water the reaction almost grinds to a halt with less than 5% yield. However, more than one equivalent to boron of water leads to increased hydrolysis of boronic acid/boroxine and catalyst deactivation.

The use of (*S*)- μ -BINAP **56** which has diphenylphosphino and bis(3,5-dimethyl-4-methoxyphenyl)phosphino groups at the 2 and 2' positions on the 1,1'-binaphthyl skeleton produced alkyl phosphonate (*S*)-**54** in 88% yield and 96% ee which is comparable to the results achieved with standard (*S*)-BINAP (84% yield, 95% ee). It is interesting to note that using (*Z*)-alkenyl phosphonate instead of the (*E*)-isomer results in the product alkyl phosphonate with the opposite configuration ((*R*)-**54**) in the presence of (*S*)- μ -BINAP. This change in configuration is also observed when (*S*)-BINAP is used with both (*E*)-**53** and (*Z*)-**53** being phenylated from the *si* face irrespective of the *E,Z*-geometry of the 1-propenyl moiety.

(S)-BINAP **55**(S)- μ -BINAP **56**

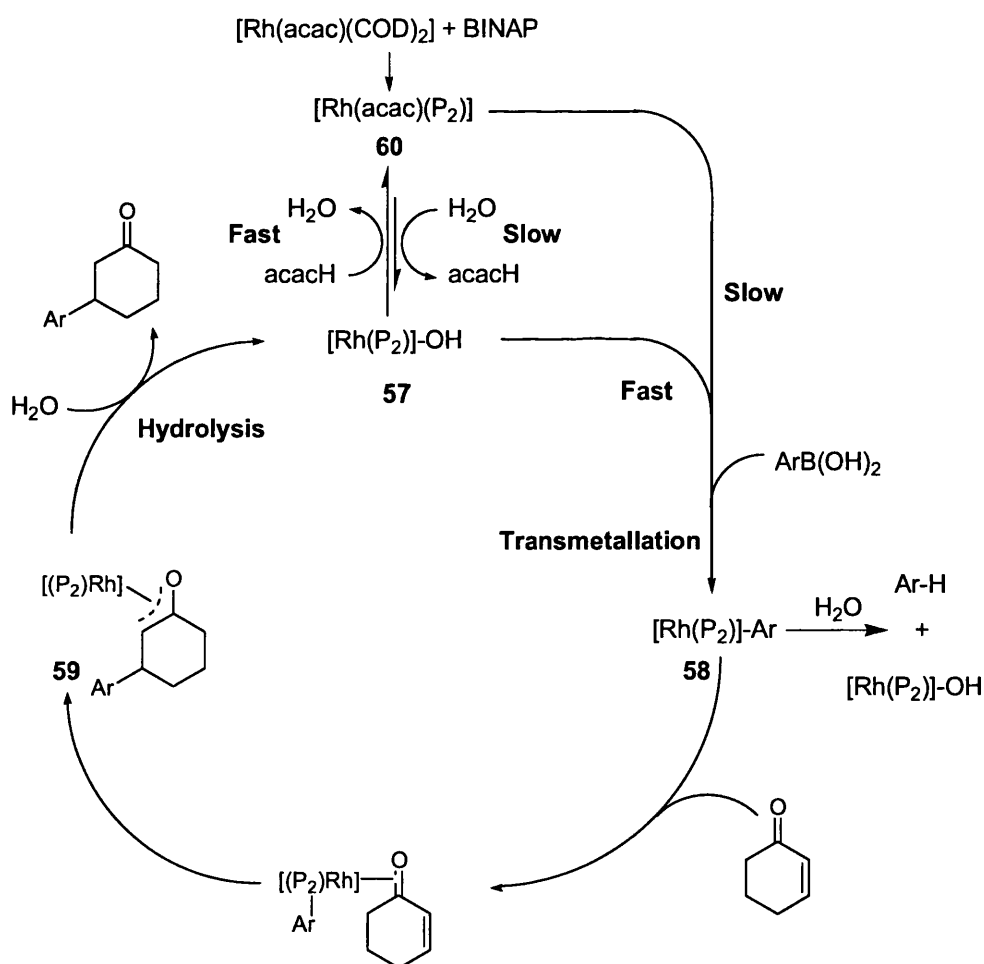
^a reaction stopped after 3 minutes.

Scheme 24

1.3 MECHANISTIC STUDIES

Hayashi recently reported a detailed insight into the important steps for the catalytic cycle of 1,4-additions to cyclohexenone. This section of the review will begin with an outline of this catalytic cycle followed by a more detailed look at the individual steps and intermediates, drawing on published experimental results.

1.3.1 Overview



Scheme 25

The catalytic cycle for the rhodium-catalysed 1,4-addition of aryl and alkenyl-boronic acids to α,β -unsaturated compounds is encapsulated above using cyclohexenone as an example.

This can be summarised using the following steps:

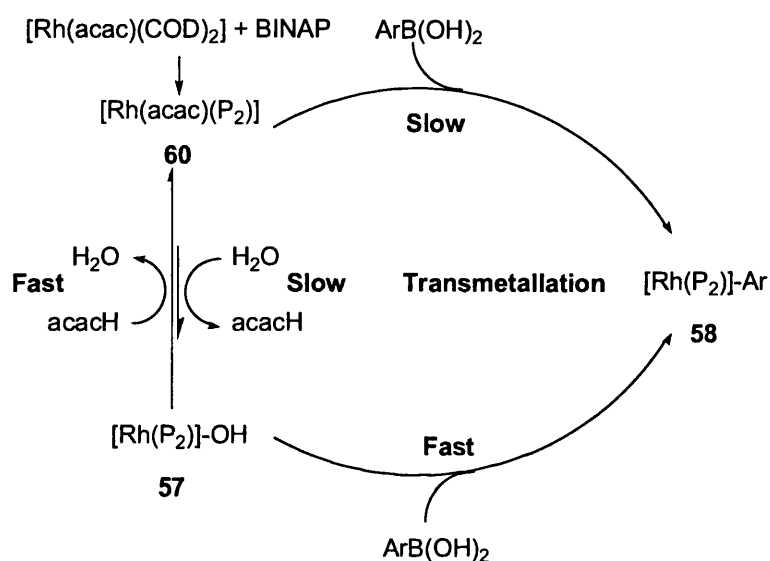
1. Formation of the active catalyst **57**
2. Transmetallation of the aryl- or alkenyl species to the rhodium centre from the boronic acid to form the phenyl rhodium **58**
3. Coordination/insertion of the enone to form the oxy- π -allylrhodium complex **59**
4. Hydrolysis of **59** to afford the desired 1,4-addition product and regenerate the active catalyst.

1.3.2 Active Catalyst Generation

The precatalyst is customarily a bis(phosphine)rhodium(I) complex with either chloride or acac as a labile ligand. Transmetallation of the boron source with this complex is typically very slow, during which time, hydrolysis of the acac complex **60** into the $[\text{Rh}(\text{OH})(\text{bis-phosphine})]$ **57** complex takes place. This complex is much more active towards transmetallation with boronic acids.

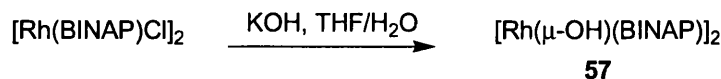
The acac ligand retards the transmetallation step due to the high stability of the $[\text{Rh}(\text{acac})]$ moiety and so $[\text{Rh}(\text{acac})]$ complexes require heating to 60°C or above for transmetallation to proceed. The use of rhodium hydroxide complexes $[\text{Rh}(\text{OH})]$ allow this reaction to proceed at lower temperatures with the transmetallation occurring at ambient temperature. This can be seen by the addition of phenylboronic acid to cyclohexenone catalysed by $[\text{Rh}(\text{OH})(\text{BINAP})_2]$ at 35°C to give quantitative yields of 3-phenylcyclohexanone which is >99% enantiomerically pure. Reaction at this lower temperature is desirable as it suppresses the hydrolysis deboronation side reaction reducing the need for excess boronic acid, furthermore, the enantioselectivity is generally higher at this temperature.

If the $[\text{Rh}(\text{OH})]$ species is formed *in situ* from $[\text{Rh}(\text{acac})]$ complex an equilibrium between these two species will be observed. $[\text{Rh}(\text{OH})]$ reacts quickly with the excess acac ligand to reform $[\text{Rh}(\text{acac})]$ which can then slowly transmetallate or slowly create the $[\text{Rh}(\text{OH})]$ species. This equilibrium has a detrimental effect on the catalyst activity leaving most of the catalyst as the ineffective $[\text{Rh}(\text{acac})]$ species. Therefore, more forceful conditions are often required for a more effective turnover, since even after being through the cycle once, rhodium may form the less active $[\text{Rh}(\text{acac})]$ species again.



Scheme 26

Evidence for the *in situ* generation of a $[\text{Rh}(\text{OH})]$ complex can be found in stoichiometric and catalytic transformations. Hayashi has shown that the treatment of $[\text{Rh}(\text{BINAP})\text{Cl}]_2$ with KOH in THF and water generates the hydroxo-bridged complex **57** (Scheme 27).³²



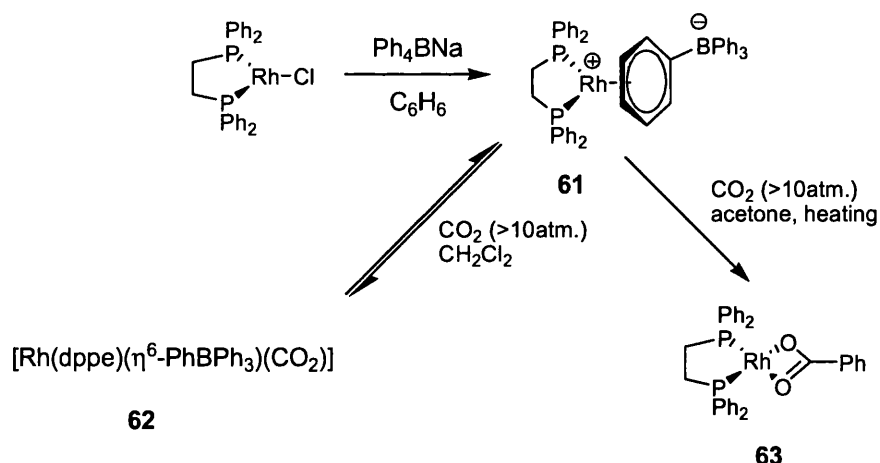
Scheme 27

Mirroring the conditions found in the majority of 1,4-addition reactions, the formation of this species in the presence of base, explains the inhibitory effects of a too acidic medium. In stoichiometric experiments the hydroxy bridged rhodium species $[\text{Rh}(\mu\text{-OH})(\text{BINAP})]_2$ undergoes complete transmetallation with phenylboronic acid at room temperature in 30 minutes. The enhanced reactivity of the rhodium hydroxo complex **57** is in part due to the high oxophilicity of boron.

1.3.3 Transmetallation

Ample evidence exists for the transmetallation of the arylboronic acid with the rhodium hydroxide species **57** in the form of many stoichiometric reactions of rhodium complexes with various organoboranes.

Aresta was the first to explore the transmetallation process between rhodium complexes and aryl organometallic reagents (Scheme 28).³³ Complex **61** was formed when $[\text{Rh}(\text{dppe})\text{Cl}]_2$ was treated with sodium tetraphenylborate in benzene. Treatment of complex **61** with >10 atm. CO_2 in DCM a new rhodium species was detected and characterised as $[\text{Rh}(\text{dppe})(\eta^6\text{-PhBPh}_3)(\text{CO}_2)]$ **62**. Once the pressure was reduced this reverted back to the original complex **61**. When complex **61** was heated in acetone under CO_2 (>10 atm.) a species bearing a benzoate ligand was formed, **63**. For this complex to arise, transmetallation of a phenyl group from the tetraphenylborate ligand must have occurred followed by insertion of CO_2 .



Scheme 28

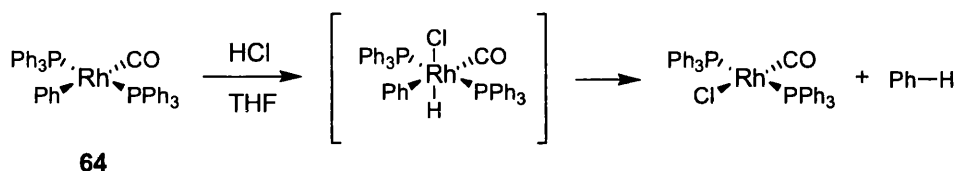
Rhodium(I) $\eta^6\text{-PhBPh}_3$ complexes formed through coordination of the aryl group to the rhodium in a η^6 -fashion have been prepared with many ligands including phosphates, bidentate and monodentate phosphines as well as a variety of olefin ligands.⁷

1.3.4 Formation of reduced aryl side product (Ar-H)

After transmetallation it is possible that the aryl-rhodium complex **58** can form the reduced aryl (Ar-H) as a side product in one of two ways (Scheme 29). Hydrolysis of the aryl-rhodium bond leads to the active $[\text{Rh}(\text{OH})]$ complex **57** being reformed and gives protonated arene, Ar-H. This occurs through coordination of water to rhodium with subsequent protonation of the Rh-C bond. Alternatively oxidative addition of water to rhodium creates a hydridohydroxyarylrhodium(III) complex which can form the reduced aryl product, through reductive elimination.

Evidence for the production of the reduced aryl product can be seen in the treatment of Vaska-type phenyl complex **64** with acetic acid which generates benzene as does treatment of the same complex with HCl (Scheme 29).³⁴ This occurs through protolytic cleavage of the rhodium-carbon bond to generate benzene. This oxidative addition/reductive elimination process has been observed with rhodium hydride

complexes with deuterated water or deuterium to generate deuterated aromatic hydrocarbons.^{35,36}



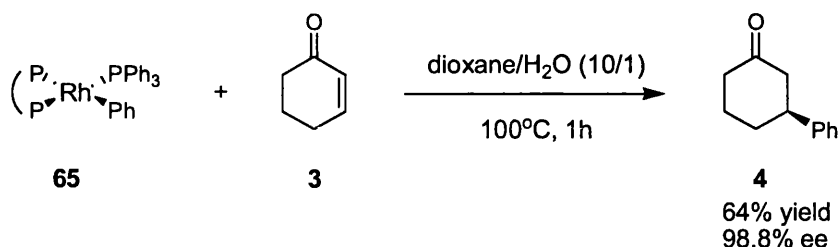
Scheme 29

In addition to water performing this reaction boronic acids themselves (or other hydroxyl containing organometallic compounds) may mediate this process. This side reaction is suppressed through either reduction of the amount of water present, lowering of the temperature or the use of other organoboranes such as boroxines and BF_3K salts.

1.3.5 Alkene Co-ordination/Insertion

Once the rhodium aryl species has been formed, facially selective coordination of the alkene occurs followed by insertion of the alkene into the Rh-C bond. This carboration produces the new carbon-carbon bond and the rhodium oxa- π -allyl species **59**. In addition to making the alkene more electrophilic, the presence of an electron withdrawing group on the olefin favours binding to the electron-rich rhodium(I) metal. This increased binding affinity of the alkene results in fewer equivalents of boronic acid being required since the coordination occurs before there is chance for hydrolysis of the aryl group. The rhodium-aryl complex then delivers the aryl nucleophile to the β -carbon of the alkene generating the oxa- π -allyl rhodium complex **59**. Protonolysis then liberates the 1,4-addition product and regenerates the active $[\text{Rh}(\text{OH})]$ complex **57**.

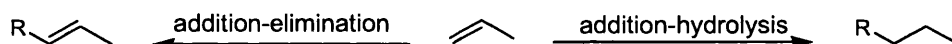
This is proven through the stoichiometric reaction of complex **65** with cyclohexenone **3** to generate the 1,4-addition product **4** with the same sense of induction and enantioselectivity as the catalytic reactions (Scheme 30).³²



Scheme 30

1.4 ADDITION TO ALKENES: ADDITION VS. HECK

The rhodium-catalysed addition of organoboranes to alkenes is more complicated since it can proceed through two paths; either, addition-hydrolysis, which produces the 1,2-addition product, or addition-elimination which produces a Heck type product (Scheme 31).

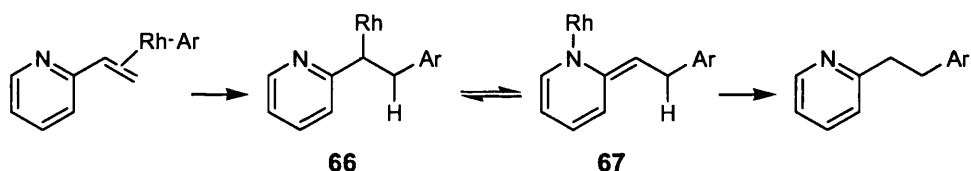


Scheme 31

Lautens has demonstrated that certain heteroaromatic alkenes can be used in 1,2-addition reactions.³⁷ For example, reaction of 2-vinylpyridine with 2.5 equivalents of phenylboronic acid and [Rh(COD)Cl]₂ with TPPDS (a water soluble phosphine ligand) in the presence of sodium dodecyl sulphate (SDS – a phase transfer reagent) in water at 80°C gives addition product in 84% yield (Scheme 33). The addition of SDS to the reaction solution results in a reduced amount of boronic acid being consumed from hydrolytic deboronation and increases the rate of the addition reaction. This was especially pronounced with the use of polar functional groups on the arylboronic acid. A variety of arylboronic acids were tested with similar results, the success of these additions being dependent on the location of the heteroatom

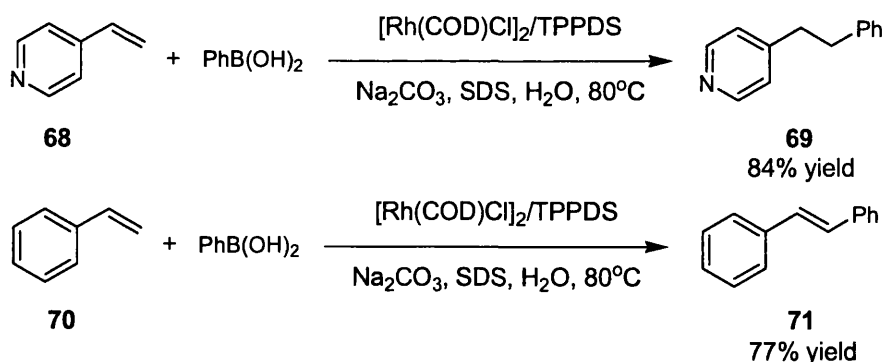
within the aromatic ring. Successful reaction occurs if the nitrogen is in the *ortho* or *para* position, however no reaction was observed with 3-vinylpyridine i.e. when the nitrogen is in the *meta* position.

This can be explained by considering the mechanism of reaction. It could be argued that coordination of *ortho*-nitrogen atom of intermediate **66** will act as a driving force stabilising the resultant complex so that hydrolysis of the rhodium-carbon bond is favoured. The successful reaction of 4-vinylpyridine (which is unable to coordinate in this manner) implies that tautomersiation of intermediate **66** to the amide **67** could occur followed by protonation to liberate product and regenerate the catalyst (Scheme 32). This is supported by the low yield when 3-vinylpyridine is used which is not capable of this tautomersiation.



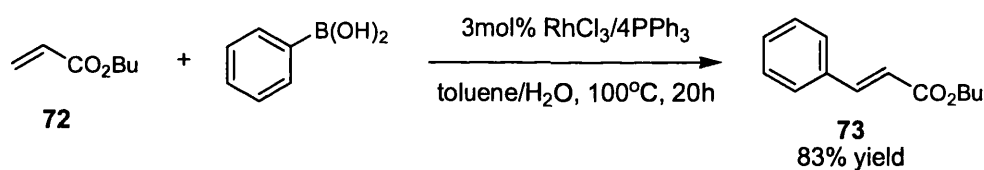
Scheme 32

However, if styrenyl olefins are used, Heck-type addition followed by β -hydride elimination occurs (Scheme 33). Olefin **70** reacted with phenylboronic acid (2.5equiv.) in the presence of $[\text{Rh}(\text{COD})\text{Cl}]_2/\text{TPPDS}$, Na_2CO_3 and SDS to give 77% yield of Heck product **71**. Most notably this reaction demonstrates that the addition reaction can occur in water despite previous reports that the presence of water accelerates deboronation, rendering the organoborane useless.



Scheme 33

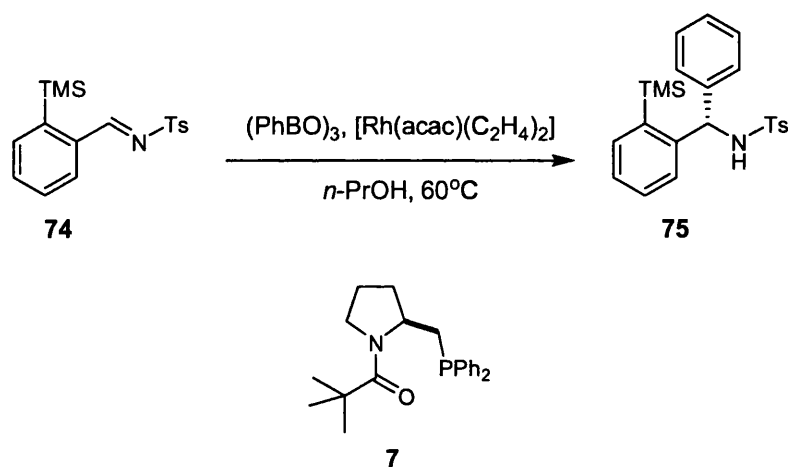
This was further demonstrated by Zou and co-workers who showed that when α,β -unsaturated compounds were reacted under the optimised conditions of RhCl_3 (3 mol%), PPh_3 (12 mol%) in toluene/water, with a 2/1 ratio of olefin/boronic acid at 100°C to produce the Heck-type product.³⁸ The olefin structure had a marked effect on the production of this product. Parent acrylate **72** (Scheme 34), reacted smoothly however substituted acrylates such as methyl methacrylate gave the α,β -unsaturated esters in only a 7% yield indicating that the steric bulk of the alkene was important. However, both electron donating and withdrawing groups on the boronic acid, proceeded to give the addition products in modest to high yields, indicating that enolisable substrates can undergo Heck-type reactions in aqueous conditions.



Scheme 34

Tomioka has extended the 1,4-addition reaction to include the addition to N-tosylarylimines **74** (Scheme 35). Chiral amidomonophosphate ligand **7** afforded a range of diarylmethylamines **75** in good yields and high selectivity when used in conjunction with $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$ in propanol at $60\text{--}100^\circ\text{C}$ for 3 hours. It was found that although phenylboronic acid gave moderate yields, the chemical yield could be further improved upon without loss in selectivity by using phenylboroxine

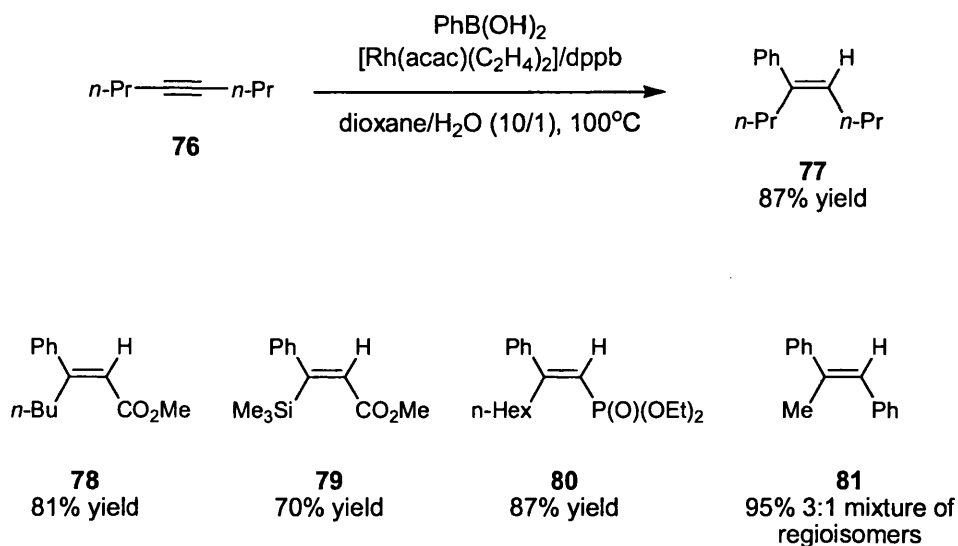
resulting in the product in 95% yield and 80% ee as opposed to the 72% yield for phenylboronic acid. Manipulation of the imine also improved selectivity as position of the substituents on the phenyl ring greatly affected selectivity with 4-Me giving 52% ee, 3-Me gave 56% ee and 2-Me gave 74% ee. As the trimethyl silyl (TMS) group can easily be converted to a proton or a halogen, 2-TMS benzaldehyde imine was prepared and reacted in high yields and selectivity (78% ee).



Scheme 35

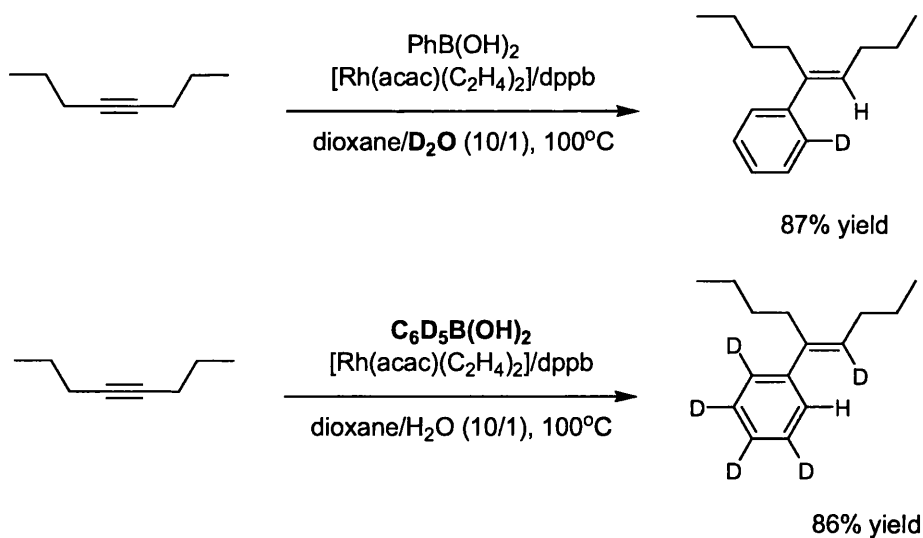
1.5 ADDITION TO ALKYNES

Rhodium-catalysed hydroarylation of internal alkynes was first described by Hayashi.³⁹ Trisubstituted alkenes were produced in high yield and isomeric purity from both activated and unactivated alkynes through the use of [Rh(acac)(C₂H₄)₂]/dppp in dioxane/water (10/1) at 100°C (Scheme 36). (*E*)-4-Phenyl-4-octene **76** was generated from 4-octyne **77** in 87% yield and >20/1 selectivity. By increasing the amount of phenylboronic acid added from 1.2 equivalents to 5, this yield can be increased to 95% with no loss in selectivity. High regioselectivities are observed with alkynes substituted with electron withdrawing groups such as esters or phosphonates for example **78**, **79** and **80**. However, unsymmetrical substrates without electron-withdrawing functionalities produce a mixture of regioisomers **81**.



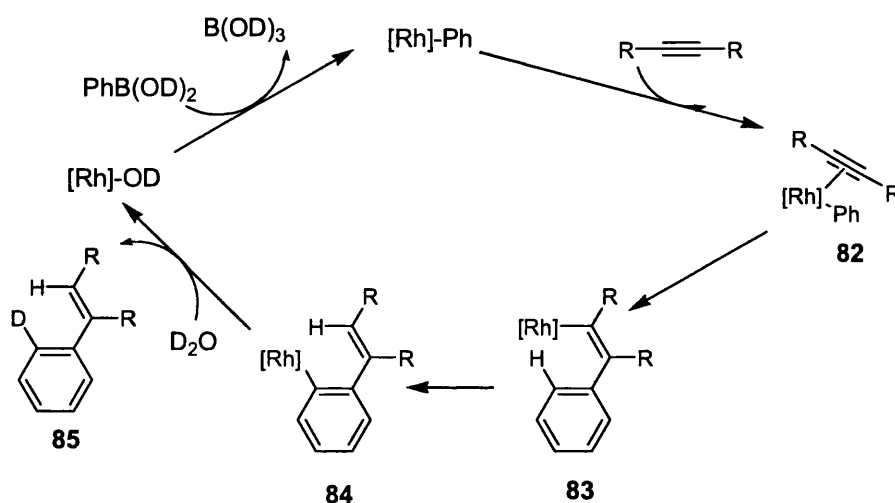
Scheme 36

Interestingly, when these reactions are run in deuterated water it is the *ortho* position of the coupled phenyl ring that is labelled and not the vinylic position (Scheme 37). Analogously, when d^5 -phenylboronic acid is used, a 1,4-deuterium shift occurs to give the vinylic deuterated alkene.



Scheme 37

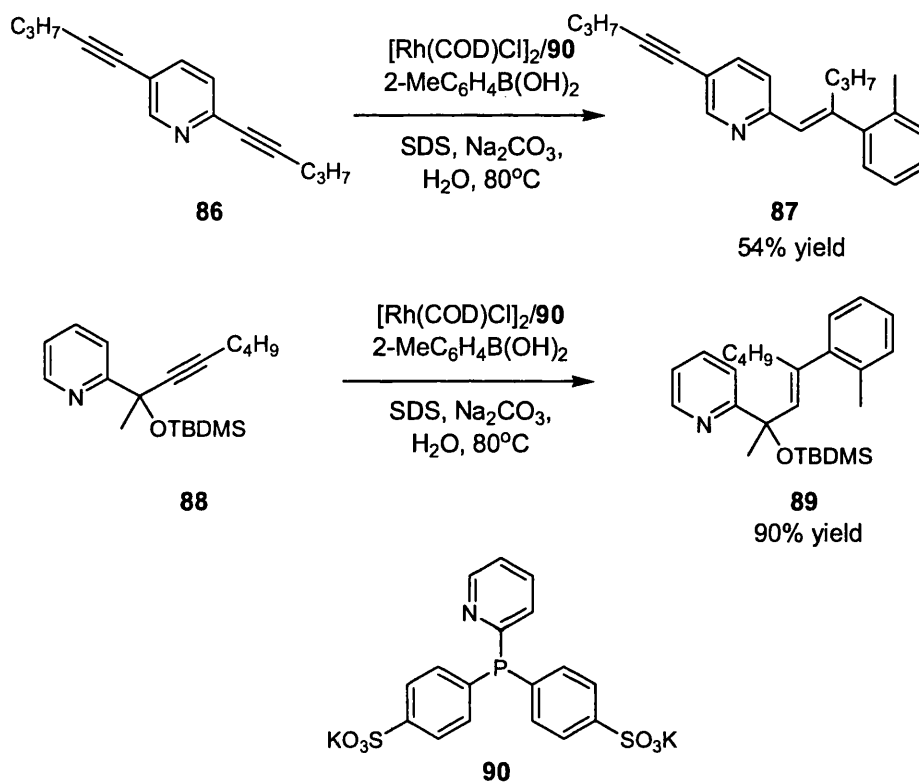
This can be rationalised by considering the mechanism (Scheme 38). Syn-carborhodation of the alkyne with the arylrhodium(I) species generates the vinylrhodium complex **83** which undergoes ortho C-H insertion on the adjacent phenyl ring producing the rhodium(III) complex **84**. Subsequent reductive elimination of the alkene and hydride ligand produces the vinylic C-H bond and a new aryl-rhodium species **84**. Hydrolysis of this gives **85** and regenerates the catalyst. A closer examination of the potential side reactions in the catalytic cycle reveals a delicate balance that is required to give **85** as the sole product. While **83** could undergo 1,4-migration, hydrolysis or reaction with another alkyne, only migration occurs. Similarly, **84** undergoes selective protonation instead of reacting with a second alkyne.



Scheme 38

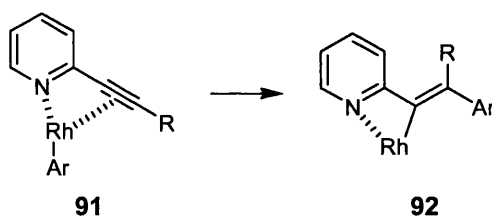
Rhodium-catalysed additions to alkynylpyridines using SDS and Na_2CO_3 were investigated by Lautens.⁴⁰ The reaction of 2-(1-hexynyl)pyridine with phenylboronic acid, performed in the presence of $[\text{Rh}(\text{COD})\text{Cl}]_2$ and ligand **90**, Na_2CO_3 and SDS in water at 80°C for 3 hours, generated the hydroarylation product in 51% yield as a single regio- and stereo-isomer. Interestingly, 3- and 4- alkynylpyridines fail to afford any product, thus the nitrogen functionality must be adjacent to the alkyne for successful reaction. This selectivity is exemplified by the reaction of **86** which

produces **87** exclusively in a 54% yield through reaction only at the alkyne adjacent to the nitrogen functionality (Scheme 39). However the alkyne need not be directly connected to the pyridine ring, for example the reaction of **88** gives **89** as the sole regio- and stereo-isomer in 90% yield.



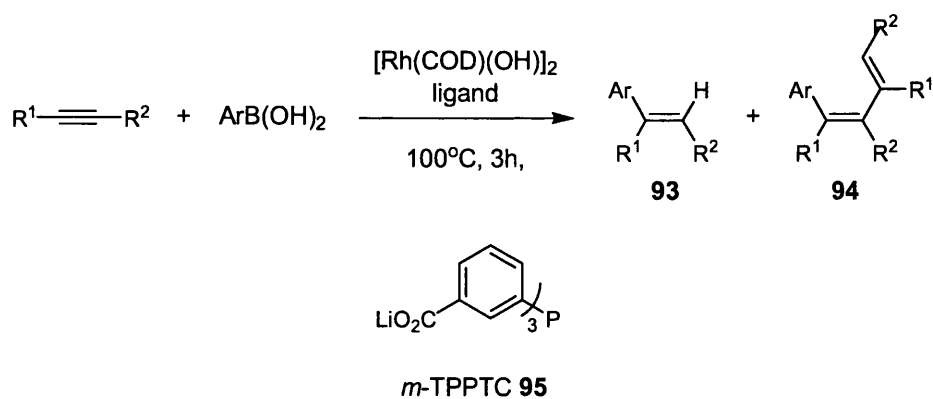
Scheme 39

By examining the mechanism the origin of this directing influence can be seen (Scheme 40). Transmetalation followed by coordination of the alkyne generates complex **91** where both the pyridine and alkyne groups are coordinated. This binding mode will result in the delivery of the aryl group to the distal alkyne carbon and formation of the alkenyl rhodium complex **92**. Protonolysis then regenerates the catalyst and liberates the product.



Scheme 40

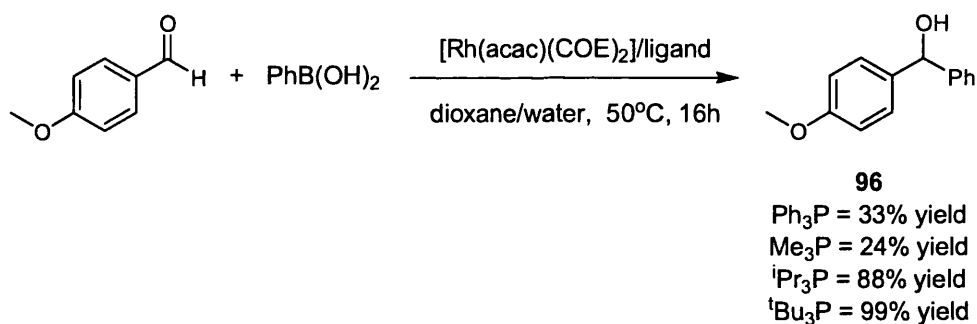
Michelet and Genet synthesised ligand **95** (Scheme 41) which they proposed would facilitate the rhodium-catalysed addition of arylboronic acids to alkynes without the need for adding SDS or base.⁴¹ Using $[\text{Rh}(\mu\text{-OH})(\text{COD})]_2$ in conjunction with ligand **95** the reaction of phenylboronic acid and oct-4-yne gave the aryl alkene in 95% yield. However this was a mixture of the desired alkene **93** and the side product diene **94** (80/20). Interestingly only a very low conversion was observed with $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$ or $[\text{Rh}(\text{COD})\text{Cl}]_2$ as the rhodium source. The use of a biphasic toluene/water (1/1) system increased the selectivity so that 99% yield of alkene **93** was observed with 100% selectivity. The diene is thought to be produced through a second oxidative addition of oct-4-yne before subsequent hydrolysis. A range of alkynes and arylboronic acids were reacted under these optimised conditions to give high yields in all cases. Furthermore, the catalyst was recycled by extracting all products from toluene and reusing the aqueous layer.



Scheme 41

1.6 1,2-ADDITIONS TO CARBONYLS

As with 1,4-additions, 1,2-addition reactions are important transformations in forming carbon-carbon bonds in organic synthesis (Scheme 42). The addition of carbon nucleophiles to carbonyl compounds can also be achieved through Barbier and Grignard reactions amongst others. However, these reactions suffer from the necessity of protecting sensitive functional groups.

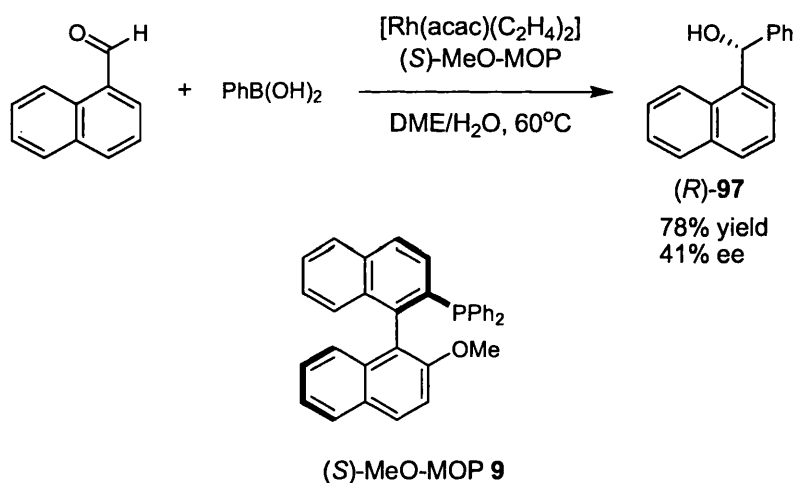


Scheme 42

$[\text{Rh}(\text{acac})(\text{CO})_2]$ in combination with a phosphine ligand has been shown to be an excellent catalyst for the 1,4-addition of arylboronic acids to enones. Miyaura *et al.* also demonstrated its ability at catalysing the 1,2-addition of arylboronic acids to aldehydes.⁴² Analogous to the findings in 1,4-additions, the reaction benefited from a large P-Rh-P angle and monodentate phosphine ligands were ineffective. The exploration of $[\text{Rh}(\text{acac})(\text{COE})_2]$ in combination with a variety of phosphine ligands lead to the hypothesis that the activity of the phosphine ligands is actually linked more to the basicity and sterics of the ligand and not solely the bite angle as previously thought.⁴³ When bisphosphanes are employed the reaction is accelerated by ligands with a large bite angle; however, with monophosphines, basic trialkylphosphines with large cone angles, such as tri-*t*-butylphosphine are better. Previously the reaction proved to be sensitive to electronic effects both in the aldehyde and the arylboronic acids; the ideal combination being electron-rich

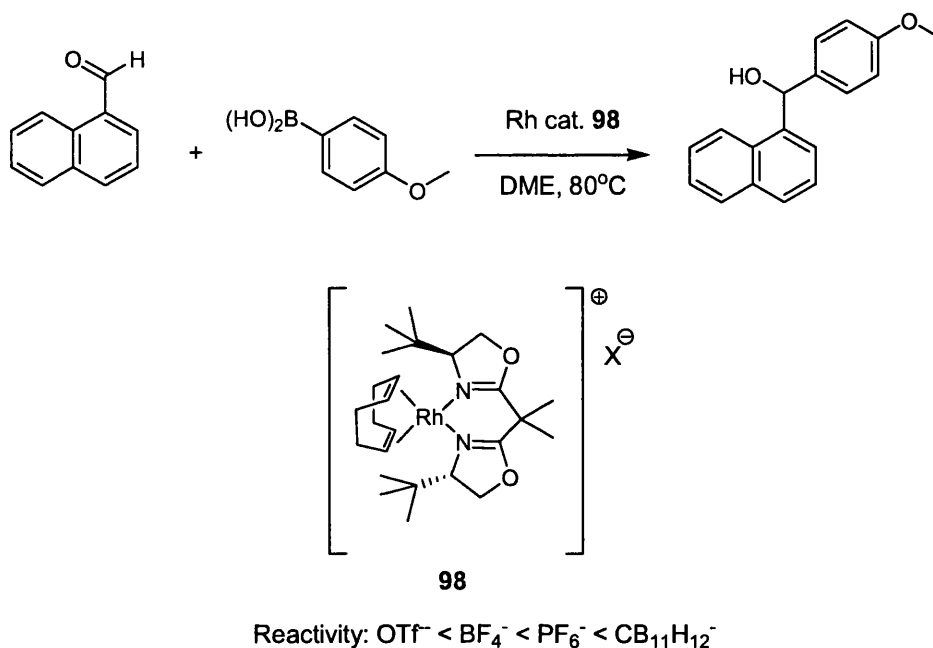
arylboronic acids and electron-deficient aromatic aldehydes. However, the heightened reactivity reduced the sensitivity of the reaction to functional groups on both the aldehyde, and the arylboronic acid.

Despite the huge success of asymmetric 1,4-additions, enantioselective 1,2-addition remains poor, with the method reported by Hayashi producing the highest ee at 41%. Surprisingly the use of BINAP and DIOP, which were highly successful in 1,4-additions, gave racemic products. The asymmetric addition to naphthaldehyde was finally achieved by the use of (*S*)-MeO-MOP **9** as ligand (Scheme 43). Treatment of phenylboronic acid and 1-naphthaldehyde with $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$ and (*S*)-MeO-MOP **9** in aqueous DME at 60°C generated the desired secondary alcohol **97** in 78% yield and 41% ee, with (*R*)-selectivity (Scheme 43).



Scheme 43

The importance of the rhodium complex counterion on the reactivity of the rhodium species was extensively researched by Frost *et al.*⁴⁴ 1-Naphthaldehyde was reacted with 4-methoxyphenylboronic acid in the presence of cationic complex **98** which incorporates a bisoxazolidinone ligand (Scheme 44). Results indicated the rate of reaction is increased with greater Lewis acidity at the rhodium centre. Weakly coordinating anions such as carboranes ($\text{CB}_{11}\text{H}_{12}^-$) achieved the best results with an 85% yield after only 2 hours.



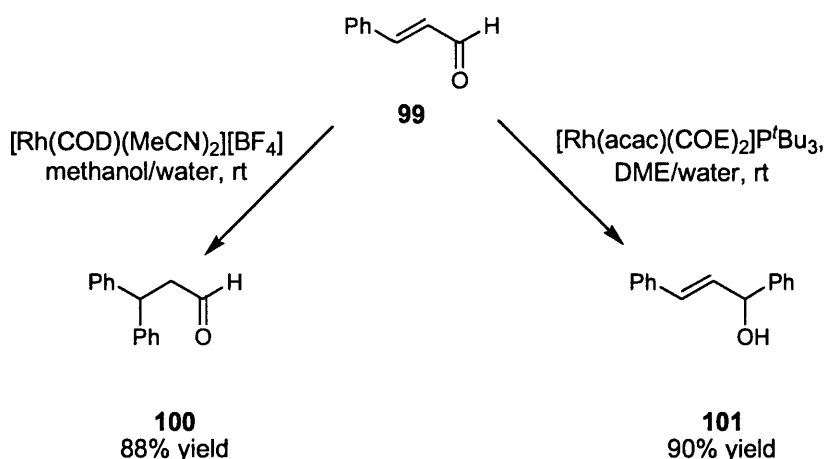
Scheme 44

1.7 1,2- VS. 1,4-ADDITION

Miyaura *et al.* noted that by adapting the conditions, boronic acids could perform either a 1,4- or a 1,2-addition to α,β -unsaturated aldehydes (Scheme 45).⁴³

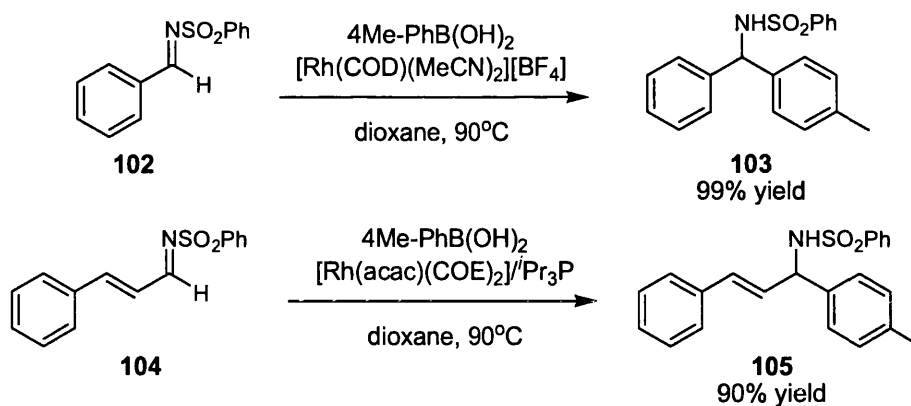
Reaction of cinnamaldehyde **99** with phenyl boronic acid in the presence of $[Rh(acac)(COE)_2]/^tBu_3P$ in DME/water (3/2) at room temperature produces **101** in a 90% yield with no sign of 1,4 addition.

The 1,4-addition reaction, however, favours the cationic rhodium complex $[Rh(COD)(MeCN)_2][BF_4]$ in the absence of ligand in methanol/water (6/1) at room temperature which gives exclusively **100** in 88% yield. However if the temperature is raised to just 50°C a mixture of products is formed.



Scheme 45

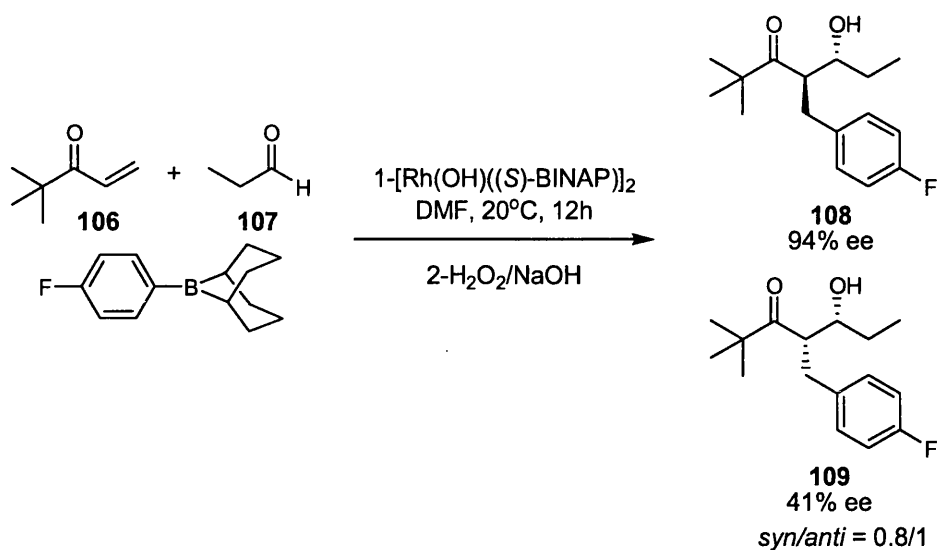
The analogous 1,2-addition to aldimines has been reported. Initial experiments of the addition of boronic acids failed to give the desired amine due to hydrolysis of the imine to the aldehyde with subsequent 1,2-addition to form the alcohol.⁴⁵ Tetraphenyl borate was a viable substitute for boronic acids, with all four phenyl groups transferred from the borane to the aldimine, using the cationic rhodium salt $[\text{Rh}(\text{COD})(\text{MeCN})_2][\text{BF}_4]$ and dppb as ligand in anhydrous conditions. Although good outcomes were obtained with N-sulfonyl and benzoyl aldimines, *n*-butyl, benzyl and phenyl aldimines produced less than 10% conversion. As the best results are achieved with electron deficient aldimines, it can be assumed that the reaction proceeds through nucleophilic attack of the aryl group on the C=N bond. Due to the higher stability of N-sulfonyl aldimines to hydrolysis and their greater reactivity, Miyaura found it was possible to react them with boronic acids in anhydrous conditions (Scheme 46).⁴⁶ Treatment of **102** with $[\text{Rh}(\text{COD})(\text{MeCN})_2][\text{BF}_4]$ and two equivalents of 4-tolylboronic acid generated **103** in 99% yield. Arylboronic esters can also be employed, but must be used in conjunction with triethylamine to obtain high yields. Interestingly, α,β -unsaturated imines could also be reacted to produce the 1,2-addition product **105** in the presence of $[\text{Rh}(\text{acac})(\text{COE})_2]$ and $^t\text{Pr}_3\text{P}$.



Scheme 46

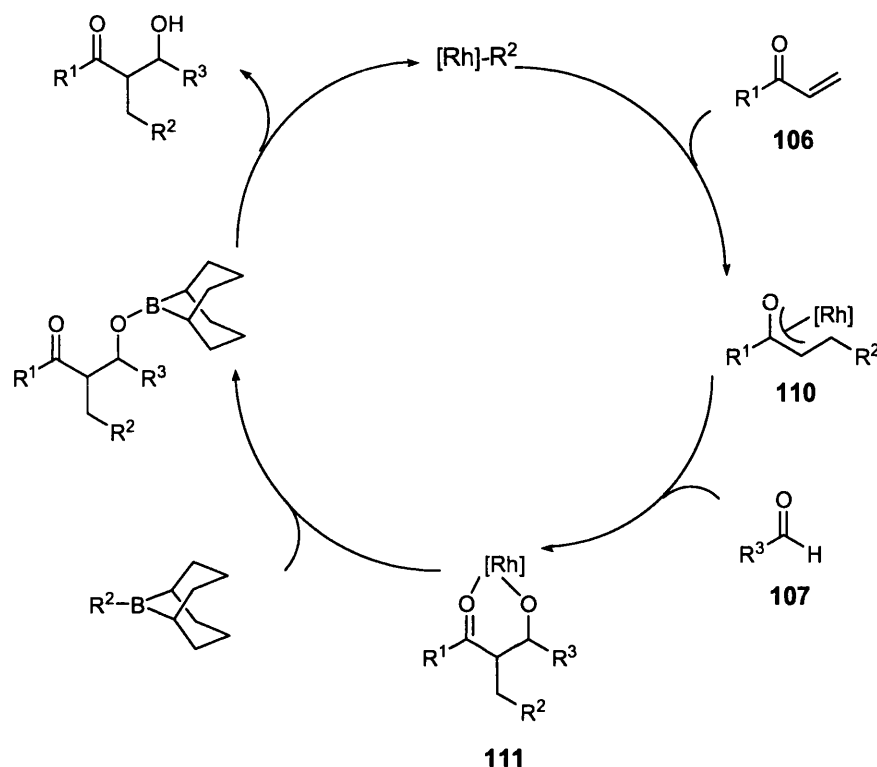
1.8 TANDEM REACTIONS

Further to Hayashi's work with *B*-Ar-9BBN (Scheme 9) it was found that the intermediate boron enolate could be coupled with an aldehyde.⁴⁷ This has been termed a tandem 1,4-addition-aldol reaction. The reaction of *B*-Ar-9-BBN, vinyl ketone **106** and aldehyde **107** catalysed by 3mol% of $[\text{Rh}(\text{OMe})(\text{COD})]_2$ proceeded in toluene at 20°C to give a high yield of the aldol-type product with high syn selectivity (Scheme 47). Changing the catalyst to $[\text{Rh}(\text{OH})((S)\text{-BINAP})]_2$ gave optically active products *syn*-(4*S*, 5*R*)-**108** in 41% ee and *anti*-(4*R*, 5*R*)-**109** in 94% ee.



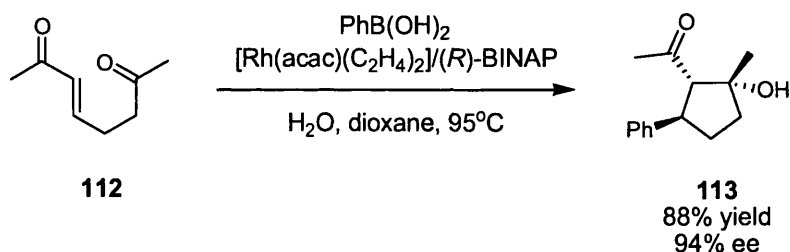
Scheme 47

Although the *syn* selectivity is low, the formation of the enantiomerically enriched products demonstrates that the reaction proceeds through an (oxa- π -allyl) rhodium complex **110** which is formed by the carborhodation of the vinyl-ketone **106** (Scheme 48). This undergoes aldol-type reaction with aldehyde **107** forming rhodium aldolate **111**. If the boron-enolate intermediate was formed first, it would require transmetallation after the carborhodation of the vinyl-ketone but before the aldol reaction leading to a racemic product. Hence, the enantiomerically enriched products point to the formation of intermediate **111**.



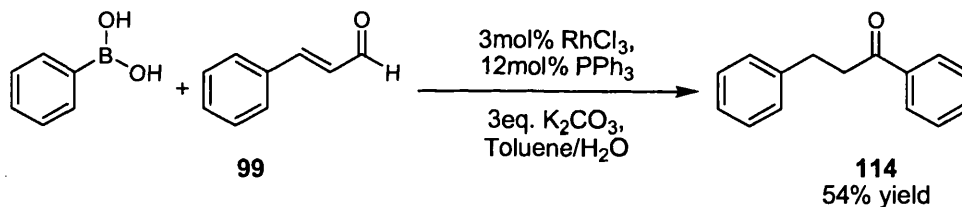
Scheme 48

This protocol has since been extended by Krische to an intramolecular tandem-1,4-addition-aldol reaction.⁴⁸ This was achieved through the use of ketone-enones such as **112** producing the cyclic product **113** in high yields (Scheme 49). These conditions were similar to the original Hayashi conditions of $[Rh(acac)(C_2H_4)_2]/BINAP$ in dioxane/water at $100^\circ C$ than the tandem 1,4-addition aldol conditions of above. In the use of $[Rh(acac)(C_2H_4)_2]/(R)-BINAP$, water is required to form the more reactive catalyst. This normally brings with it the problems of protonolysis. However this reaction can take place in the presence of an excess of water (five equivalents) as the intramolecular reaction of the intermediate with the ketone moiety is faster than the protonolysis by water.



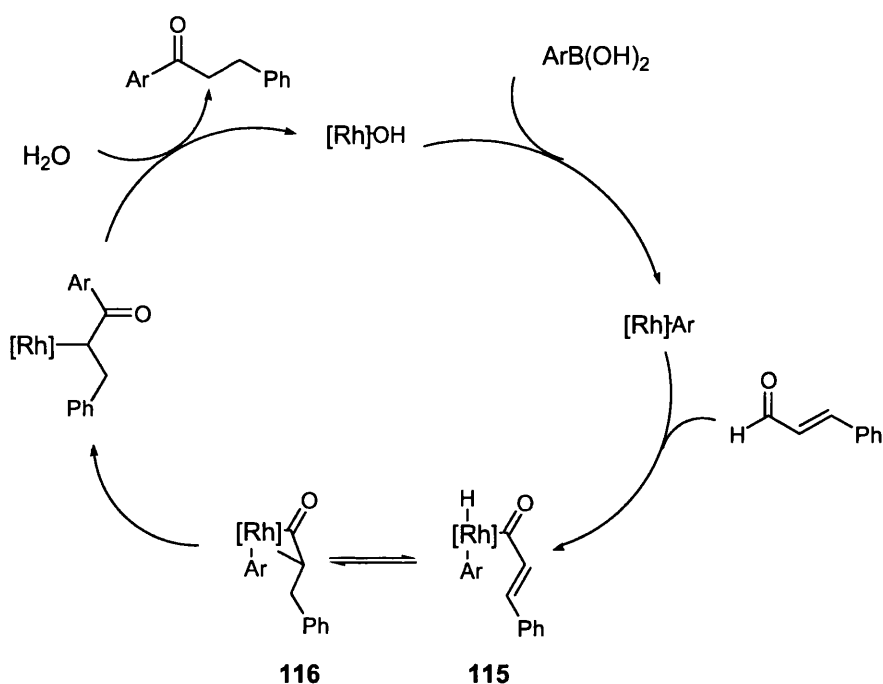
Scheme 49

Zou found that reacting cinnamaldehyde **99** with boronic acid in biphasic conditions of RhCl_3 in combination with 4 equivalents PPh_3 and potassium carbonate in toluene/water at reflux yielded neither the 1,4-addition nor the 1,2-addition product, however a conjugate addition/cross coupling tandem reaction was found to occur (Scheme 50).⁴⁹ Reaction of cinnamaldehyde **99** with phenylboronic acid gave 54% yield of β -phenylpropiphenone **114**.



Scheme 50

The mechanism is thought to proceed via transmetallation followed by oxidative addition of the C-H of the aldehyde group into the Rh-C(aryl) bond (Scheme 51). Intramolecular insertion of the C=C to Rh-H affords the ketene complex **115**. Reductive elimination then ensues to release the strained intermediate **116**, which then undergoes oxidative addition of water to release the product and afford the reactive catalyst.



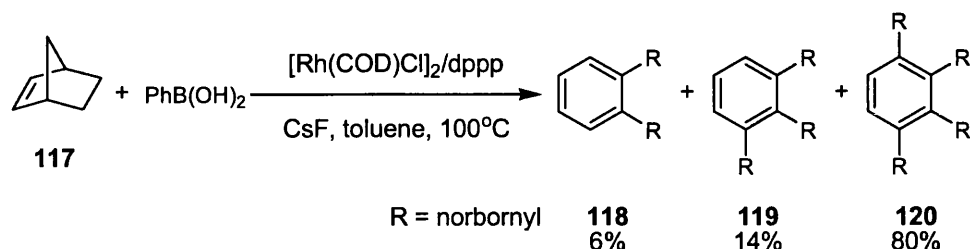
Scheme 51

Evidence for this can be observed using deuterated water as the co-solvent, leading to deuteration of the product at the α -position, indicating the hydrolysis of the Rh-C bond being involved. Using the deuterated aldehyde of cinnamaldehyde lead to β -deuterated product, indicating the C=C is self-reduced by the proton from the aldehyde. A number of arylboronic acids and cinnamaldehydes were able to react with moderate yields achieved in all cases.

1.9 RING OPENING REACTIONS

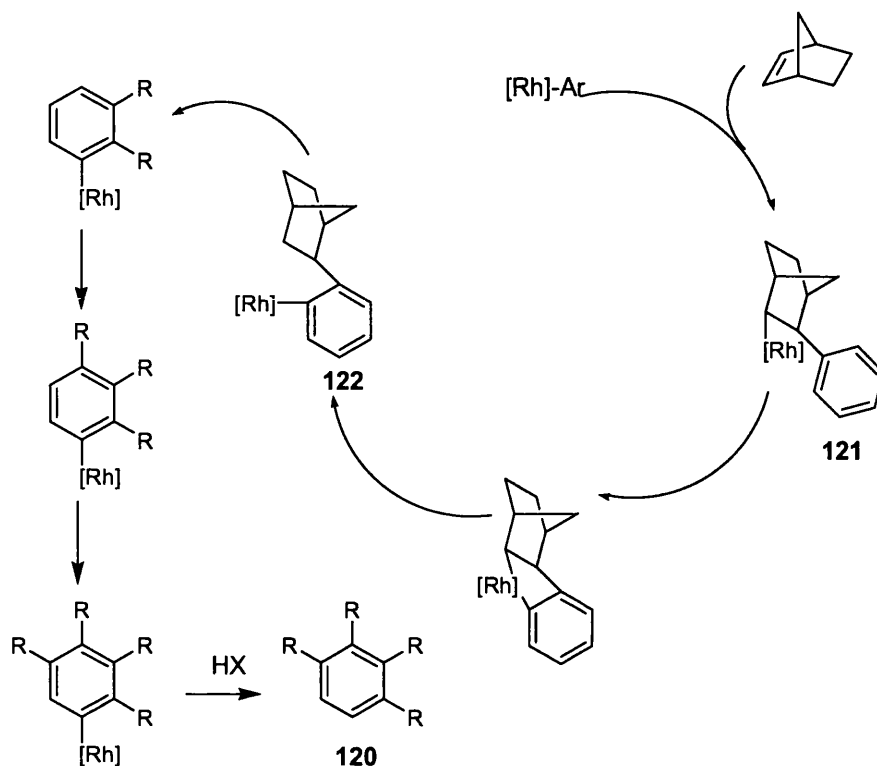
Miura's research has explored transition metal catalysed domino or 'merry-go-round' sequential allylations. The addition of arylboronic acids to the strained alkene, 2-norbornene **117**, was shown during this research to result in a tetra-alkylated arene **120** as the major product (Scheme 52). This is achieved through addition of phenylboronic acid in the presence of seven equivalents of norbornene **117**, two equivalents cesium fluoride, and $[\text{Rh}(\text{COD})\text{Cl}]_2/\text{dppp}$ at 100°C in toluene. Reducing

the number of equivalents of norbornene increases the amount of 1,2-di and 1,2,3-tri-(2-norbornyl)benzenes **118** and **119** products could be increased.



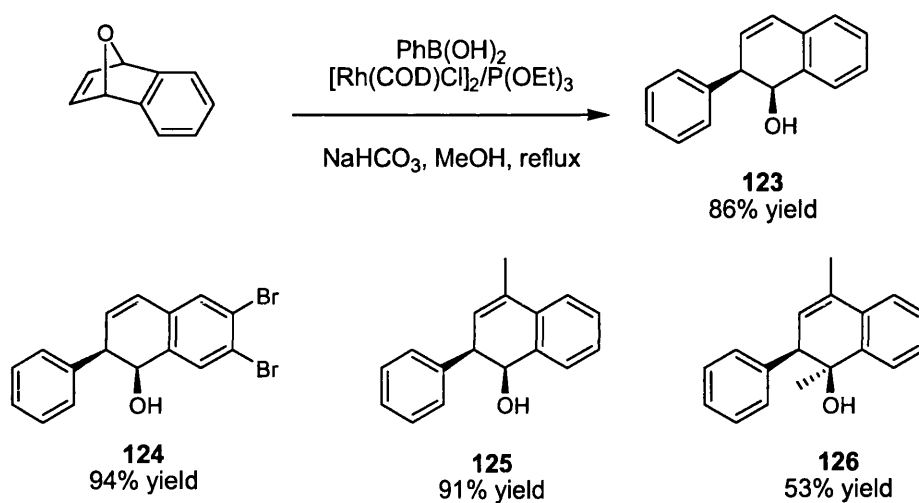
Scheme 52

This ‘merry-go-round’ multi addition reaction is thought to be due to the lack of water, the presence of which would hydrolyse the intermediate complex to the product before a further allylation can occur. Initial transmetallation generates the rhodium phenyl complex that coordinates to the exo face of norbornene (Scheme 53). Insertion of the alkene then leads to intermediate **121**, which in the absence of a β -hydrogen to eliminate generates **122** through ortho C-H insertion followed by reductive elimination. This whole process can then occur up to three more times. After the third cyclorhodation step there is too much steric bulk around the arene to facilitate a further insertion of norbene, thus the unfavoured protonolysis step will occur to generate **120** and regenerate the active catalyst.



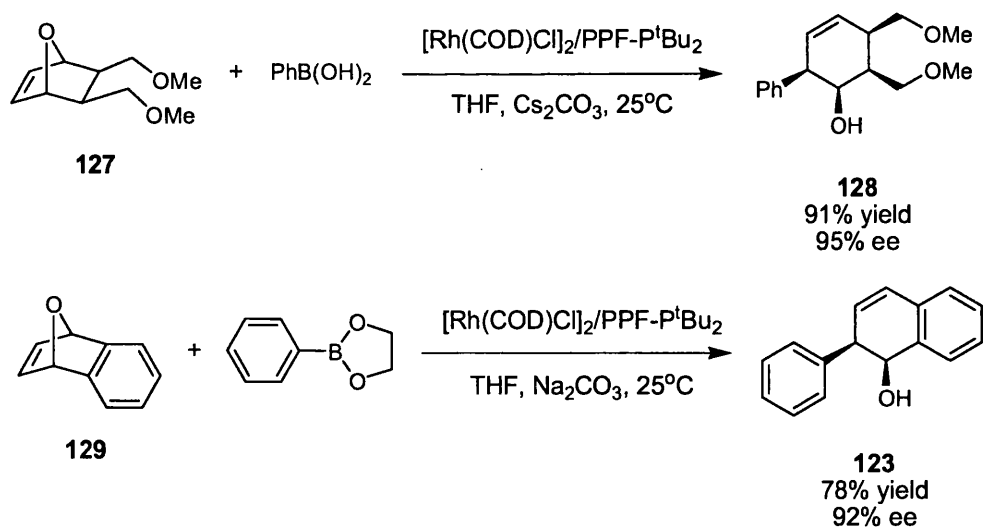
Scheme 53

Aryl and alkenylboronic acids can also be added to oxabenzonorbornadienes through ring opening across the bridging oxygen. Murakami achieved the best results using a combination of $[Rh(COD)Cl]_2$ and two equivalents of $P(OEt)_3$ and two equivalents of $NaHCO_3$ in methanol at reflux yielded alcohol **123** in 80% yield (Scheme 54).⁵⁰ A variety of oxabenzonorbornadienes reacted smoothly, with the most noteworthy being the toleration of bromine on the aromatic ring (**124**) and the formation of **125** that demonstrates unsymmetrical substrates are able to react with high diastereoselectivity. The yield did however drop when two bridgehead methyl groups were present, such as **126** but the yield is still respectable at 53%.



Scheme 54

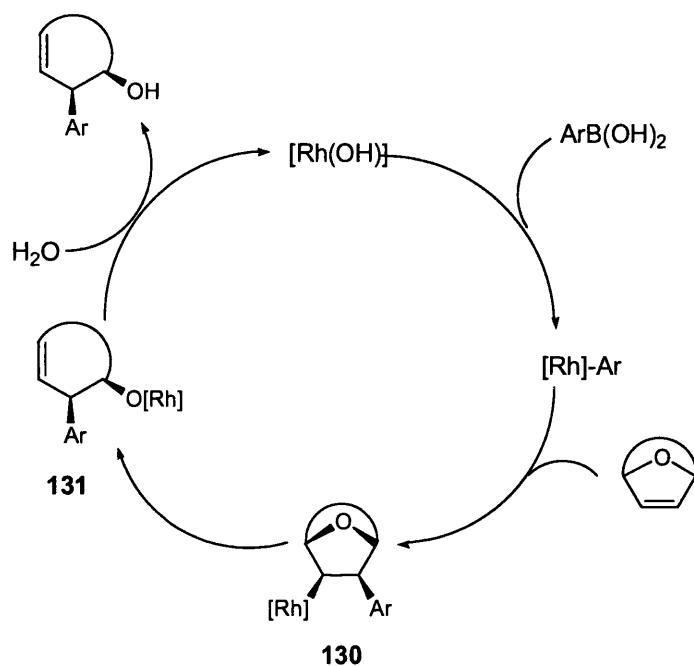
In 2002, Lautens *et. al.* reported modified conditions that afforded these types of alcohols with good yields (71-95%) and enantioselectivities (92-95%) (Scheme 55).⁵¹ Treatment of **127** with phenylboronic acid, aqueous cesium carbonate and $[\text{Rh(COD)Cl}]_2/\text{PPF-P}^t\text{Bu}_2$ in THF at room temperature produces **128** in 91% yield and 95% ee as a single isomer. A range of boronic acids proved compatible, including vinyl species as well as aryl groups containing iodide functionalities, with high enantioselectivity achieved for all.



Scheme 55

Although these optimised conditions were unsuccessful for the addition of phenylboronic acid to oxabenzonorbornadiene **129**, exchange of the boronic acid for phenylboronic ethylene glycol afforded **123** in 78% yield and 92% ee (Scheme 55).

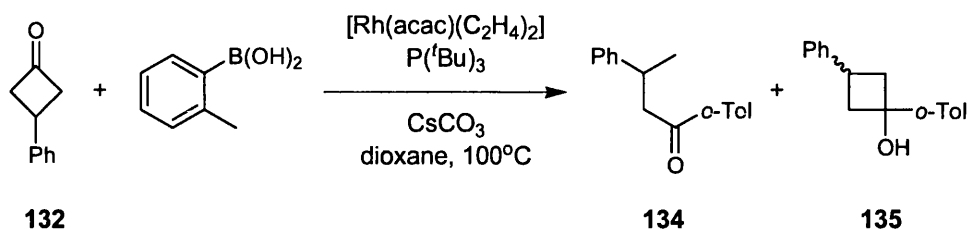
Murakami and Lautens independently proposed similar mechanism for these ring-opening reactions, an outline of which is depicted in Scheme 56.^{50,51} Initial formation of the active $[\text{Rh}(\text{OH})]$ complex is followed by transmetalation of the organoboronic acid to the rhodium followed by the coordination of the oxabicyclic through the sterically more accessible exo-face. Insertion of the alkene into the Rh-C bond generates complex **130** from where β -oxy-elimination proceeds to regenerate the olefin and to form an alkoxyrhodium species, **131**, which undergoes protonolysis producing the alcohol and regenerating the active catalyst.



Scheme 56

Murakami postulated that an arylrhodium(I) species is more electron rich than a rhodium(I) halide or a cationic rhodium(I) species and so more easily oxidised to a rhodium(III) species during insertion between the carbonyl and α -carbons.⁵² From this it was proposed that addition of phenylboronic acids to cyclobutanones would result in an addition/ring opening mechanism resulting in the formation of a butyrophenone derivative (Scheme 57). Reaction of 3-phenylcyclobutanone **132** with *o*-tolylboronic acid in the presence of $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]\text{P}(\text{tBu})_3$ and cesium carbonate resulted in the formation of 90% butyrophenone derivative (resulting from the cleavage of the C(acyl)-C(α) bond and bonding of the *o*-tolyl group to the acyl carbon) and 10% tertiary cyclobutanol **135** (resulting from addition of the *o*-tolyl group to the carbonyl group) after 3 hours (Scheme 57). After 24 hours no tertiary cyclobutanol was detected suggesting that **135** isomerises into **134**. However this isomerisation/ring opening process does not happen when **135** is heated in the absence of catalyst. This led them to believe the mechanism to be *via* the addition of arylrhodium to the carbonyl group of **132** followed by the ring opening of the

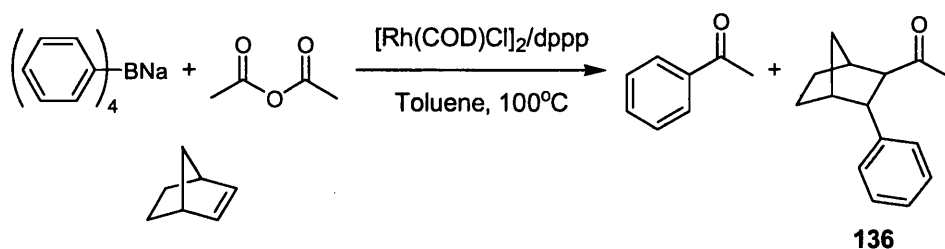
resulting rhodium alcoholate through β -carbon elimination, rather than *via* direct insertion of rhodium(I) between the carbonyl carbon and the α -carbon.



Scheme 57

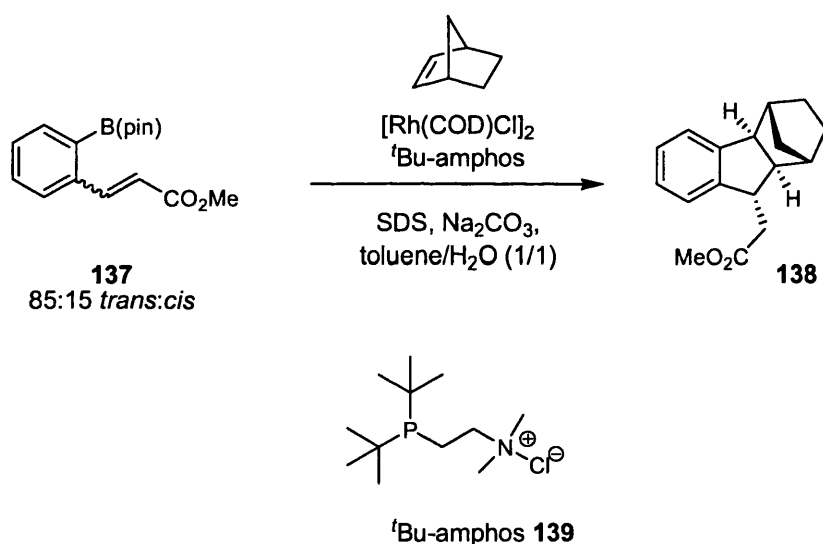
1.10 MISCELLANEOUS REACTIONS

Miura has reported the reaction of tetraarylborates with anhydrides to produce simple ketones (Scheme 58).⁵³ $[\text{Rh}(\text{COD})\text{Cl}]_2/\text{dppf}$ catalysed the reaction of acetic anhydride with tetraphenylborate in toluene at 100°C to furnish 91% acetophenone after two hours. This was then extended to include a three-component coupling reaction of acetic anhydride, tetraphenylborate and norbornene. Using identical conditions, acetophenone was produced along with 60% of **136** through the three-component pathway. This product is created through transmetallation followed by insertion of the norbornene alkene into the Rh-C(aryl) bond. Oxidative addition of the anhydride followed by reductive elimination generates product **136** and regenerates the active catalyst.



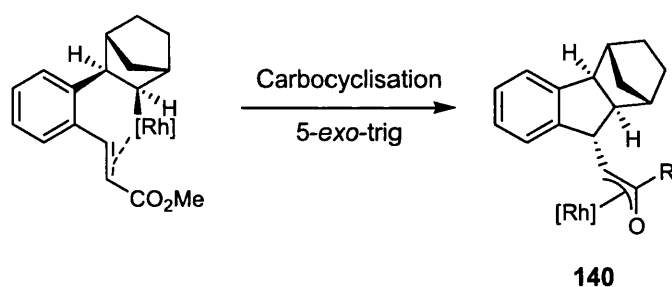
Scheme 58

Lautens has demonstrated the synthesis of indanes through reaction of norbornene and conjugated alkenyl boronic esters.⁵⁴ The reaction of nobornene with boronic ester **137** catalysed by $[\text{Rh}(\text{COD})\text{Cl}]_2$ in the presence of SDS and water resulted in the product in poor conversion. However, on addition of the water soluble ligand TPPDS and using toluene/water (1/1) as solvent, a 100% conversion was achieved, but unfortunately this constituted of a mixture of the two possible products. Switching to the more electron-rich and bulky water soluble ligand **139** ('Bu-amphos) resulted in a 95% conversion of solely the indane product **138** which was itself in a >20:1 diastereomeric ratio (the stereochemical configuration was assigned by 2D NMR and NOE experiments) (Scheme 59). This shows that the amphos ligand is responsible for the high activity and selectivity seen.



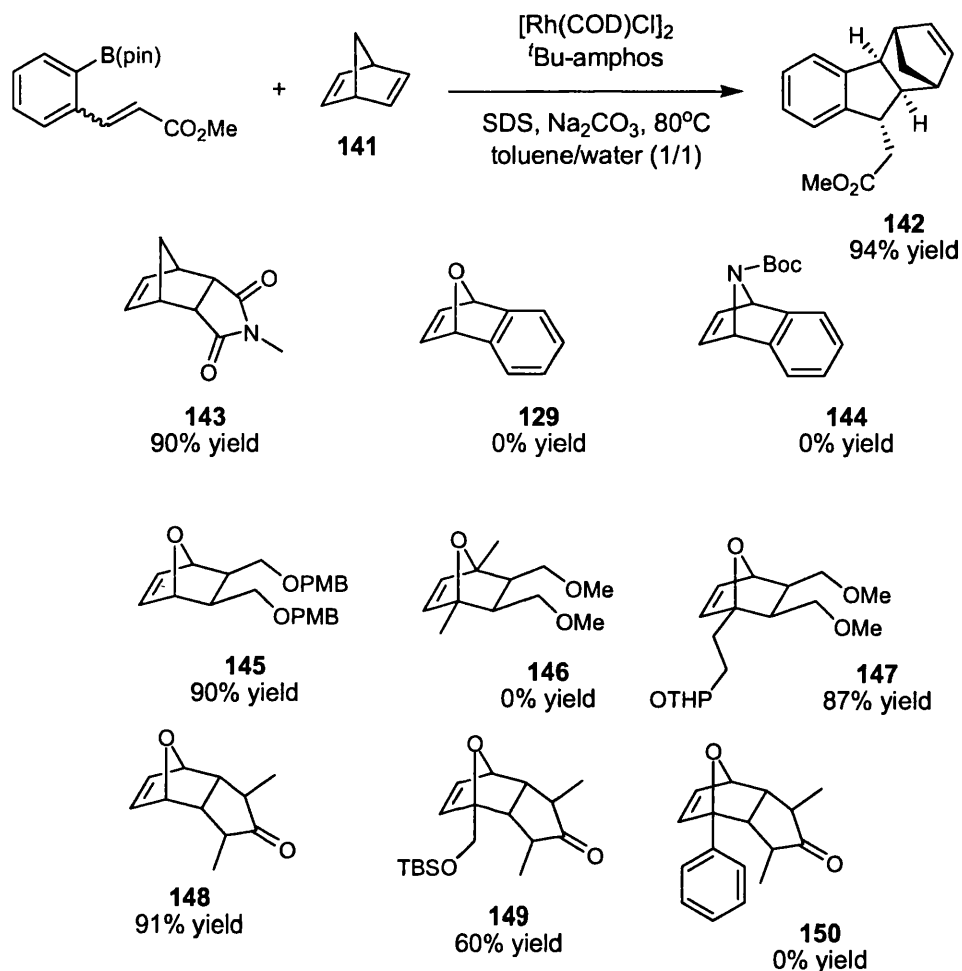
Scheme 59

The mechanism is thought to follow transmetalation of the borane followed by carboration of the norbornene subsequent carbocyclisation *via* a 5-exo-trig process generated the rhodium enolate **140** before protodemetalation afforded the product and regenerated the active catalyst (Scheme 60).



Scheme 60

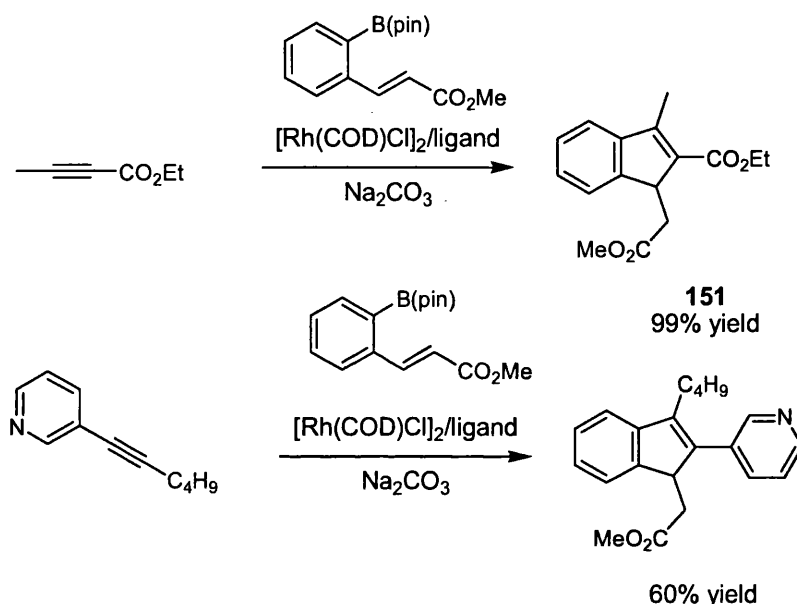
In an extended paper, Lautens further explored this carbocyclisation through examination of norbornyl derivatives such as norbornadiene **141** which reacted well to give >90% yield of product **142** (Scheme 61).⁵⁵ Surprisingly oxabenzonorbornadiene **129** inhibited the reaction leading to no product, this is thought to be due to oxidative addition into the strained C-O bond. This lack of reactivity is mirrored by the azabicyclic system **144**, which also does not react. Although **145** proved to react well (90% yield) when substituents were introduced onto the bridgehead carbons, there were varied results. Disubstituted **146** did not react at all, but norbornene **147** with only one substituent present, afforded the product as a single diastereomer and regioisomer **147** in 87% yield. This is thought to be due to the shielding of the alkene by the bridgehead substituents, this sensitivity is increased when **150** is used, which has a large phenyl group substituents resulting in no reaction. However, reducing the size of the substituents, results in 60% yield of the single regio- and diastereo-isomer if **149** is used.



Scheme 61

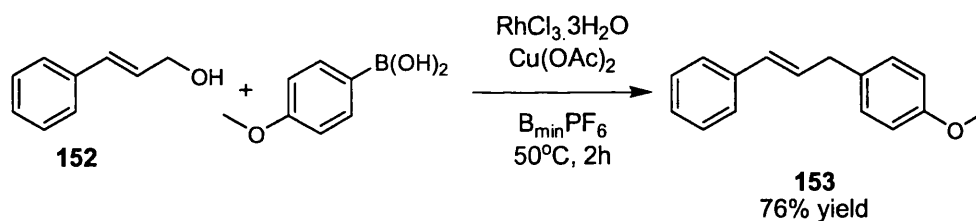
Carbocyclisation has been further explored by Lautens (Scheme 62), here, rather than a strained alkene, alkynes were explored as coupling partners.⁵⁶ It had been previously reported that when using alkenes such as styrene no reaction was achieved. Unfortunately, utilising the previous conditions only 25% yield of product **151** was obtained. However, by changing the conditions to [Rh(COD)Cl]₂ in combination with tri-*t*-butylphosphonium tetrafluoroborate and performing the reaction in dioxane/water (10/1) yielded 99% of product **151** after three hours. An electron-withdrawing group on the alkyne proved essential, with alkynes containing either a phenyl or ester group reacting well. However, if both groups were present i.e. one on each side the yield was reduced due to the alkyne being too electron deficient. Pyridine groups were explored as possible electron-withdrawing groups

and reacted well with the nitrogen in the 3- or 4-position, but no reaction was observed when in the 2-position.



Scheme 62

Kabalka *et al.* recently reported the direct aryl-allylation through the reaction of cinnamyl alcohol **152** with boronic acids catalysed by rhodium complexes (Scheme 63).⁵⁷ Cinnamyl alcohol was coupled with 4-methoxyphenylboronic acid in the presence of $[\text{RhCl}_3] \cdot 3\text{H}_2\text{O}$ and $\text{Cu}(\text{OAc})_2$ in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ($\text{B}_{\text{min}}\text{PF}_6$), thus generating the allylphenyl **153** in 76% yield. Electron-rich boronic acids were found to generate products in higher yields than those that were electron-deficient, with *ortho*- and *meta*-substituted arylboronic acids typically affording lower yields than *para*-substituted ones. Due to the use of the ionic liquid the catalyst can be recycled with no significant loss of activity. The authors propose that oxidative addition of rhodium to the C-O bond of cinnamyl alcohol forms a π -allylrhodium complex, which in turn undergoes transmetallation with the boronic acid. Reductive elimination then follows forming the desired product and regenerating the catalyst.



Scheme 63

1.11 CONCLUSION

This review has highlighted the significant advances in rhodium-catalysed additions of organoboranes in the past eight years. This progress has led to many new carbon-carbon bond forming reactions which are high yielding and often form one or two new chiral centres with significant selectivity. This combination of rhodium and organoboranes has performed an array of reactions including 1,4-addition, 1,2-addition, ring opening, and tandem 1,4-addition/aldol - frequently in demanding conditions and always demonstrating high level of tolerance to functional groups and reaction conditions. All of this places rhodium as a good contender to palladium, which dominates this area at the moment.

This direction of research is set to continue to grow with the new synthetic pathways to both old and new drug molecules requiring more tolerant and highly selective methods.

CHAPTER TWO:
Rhodium-Catalysed Acylations

2 RHODIUM-CATALYSED ACYLATIONS

2.1 AIMS AND OBJECTIVES

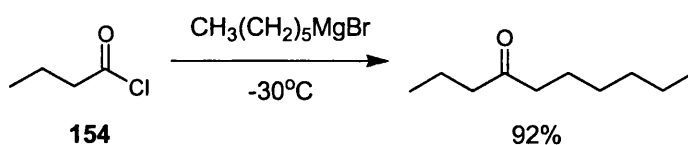
The object of this project is to exploit the rhodium/boron transmetallation process in an effort to develop a new synthetic route to ketones. This protocol is intended to compete with Friedel Crafts acylations without sustaining the same limitations incurred with some functional groups.

2.2 BACKGROUND

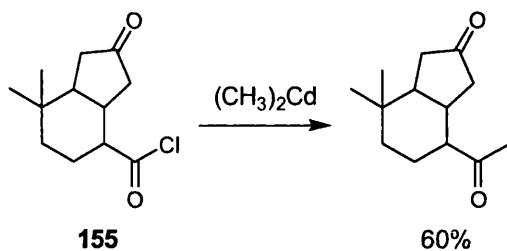
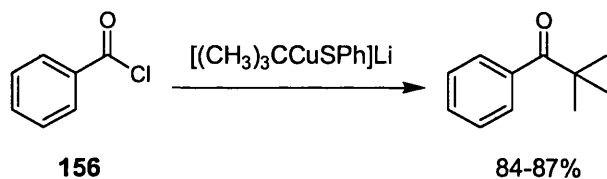
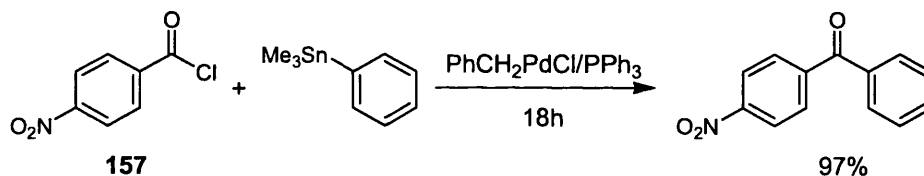
Ketones are of fundamental importance to synthetic chemistry; consequently there are a wide variety of methods available for their synthesis. Below is a brief overview of the most common methods when starting from acid chlorides **154-7**, alcohols **158-9**, alkenes **160-1**, alkyl halides **162**, alkynes **163**, simple aromatics **164**, nitriles **165**, amides **166** and anhydrides **167**. This highlights that the existing protocols for the preparation of the starting preparations are limited in both selectivity and general applicability.

A. Acid Chlorides

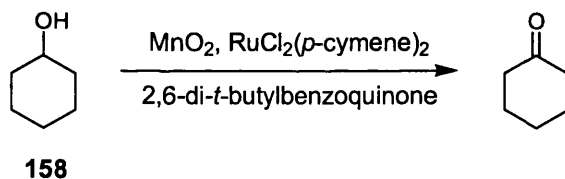
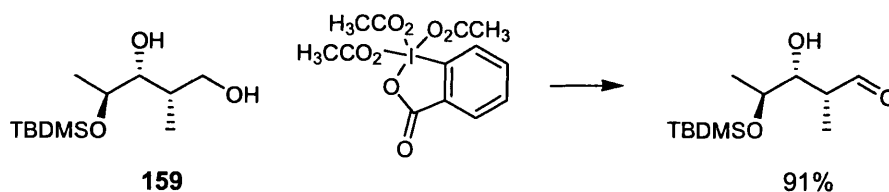
1. With Grignard Reagents.⁵⁹



Scheme 64

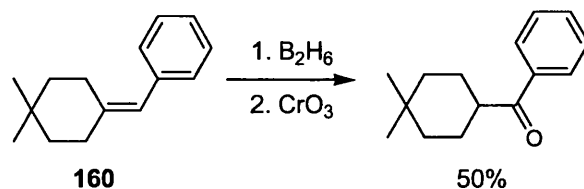
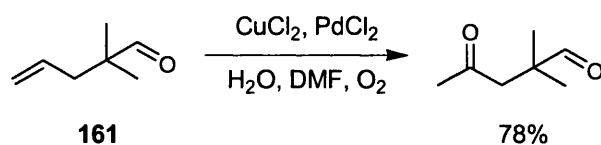
2. With Organocadmium.⁶⁰3. With Organocuprates.⁶¹4. With Organostannanes.⁶²

B. Alcohols

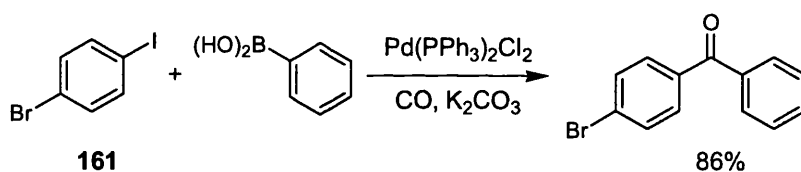
1. With Transition Metal Oxidants.⁶³2. With Other Oxidants.^{64,65}

Scheme 64 continued

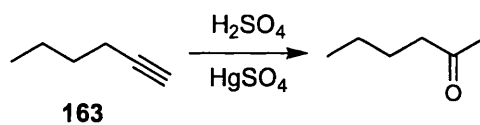
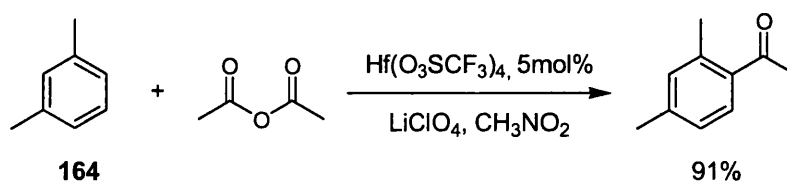
C. Alkenes

1. With organoboranes⁶⁶2. Wacker Reaction⁶⁷

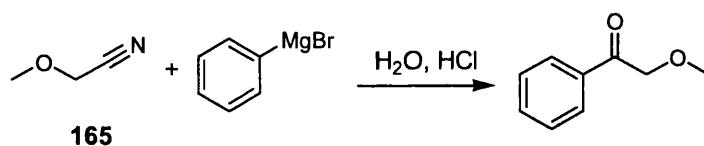
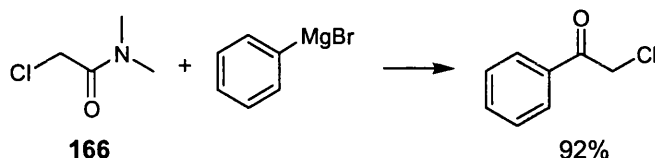
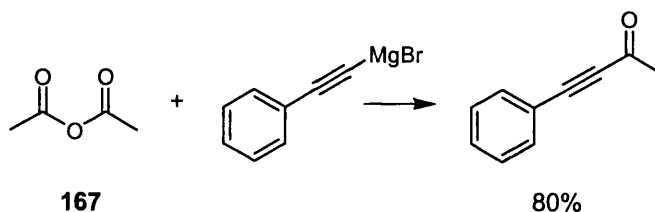
D. Halides

1. Carbonylation⁶⁸

E. Alkynes

1. Hydration⁶⁹F. Aromatics⁷⁰

Scheme 64 continued

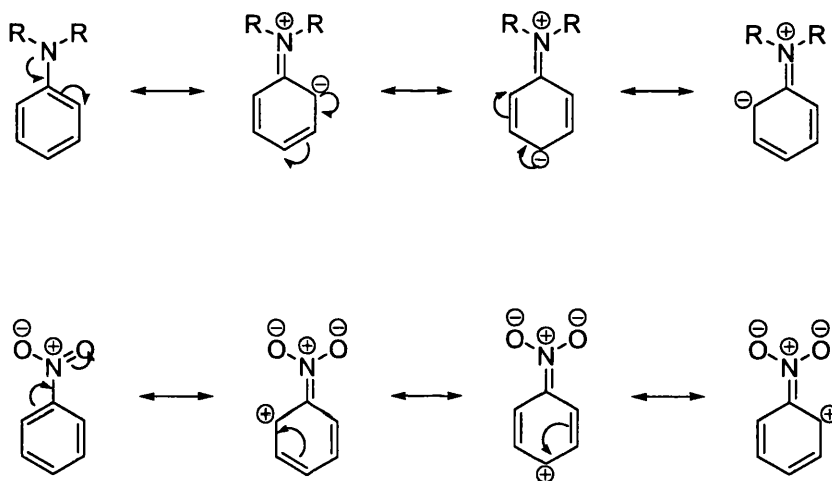
G. Nitriles⁷¹H. Amides⁷²I. Anhydrides⁷³

Scheme 64

These procedures encompass the use of Grignard and coupling reagents, as well as reactions such as Friedel Crafts acylations, oxidations and carbonylations. Despite this array there are no truly general methods, with disadvantages and limitations being seen for each method. For Grignard and oxidation systems often the product is just as reactive as the starting material meaning that careful monitoring of conditions must be used to ensure the reaction stops at the required product. Organocadmium reagents are very toxic and so should be avoided whilst organolithium-cuprates are unstable and cannot be stored for extended periods.

Due to the nature of Friedel Crafts acylations, the presence of certain functional groups can dramatically affect the efficiency of the reaction. If an electron-withdrawing group is present, the electron-deficient aromatic ring will be less reactive and in the case of nitrobenzene will not react at all. On the other hand electron-donating groups enhance the reactivity and the reactions proceed faster with a greater overall yield. The regioselectivity of the reaction is also largely dependent

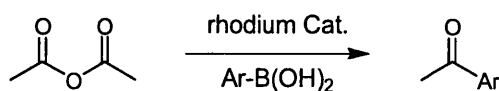
on the resonance forms of the reactive intermediate. As can be seen in Scheme 65 electron-withdrawing groups will direct the acyl group to the *meta* position and electron-donating groups direct the acyl group to *ortho* and *para* positions - often leading to a mixture of products. In general *para* attack predominates for alkyl benzenes but the percentage *ortho* attack increases with the electrophilicity of the acylium ion; as much as 50% *ortho* product is observed with formylium and 2,4-nitrobenzoylium. Both of these effects in combination cause serious limitations to this method.



Scheme 65

2.3 PROPOSED REACTION

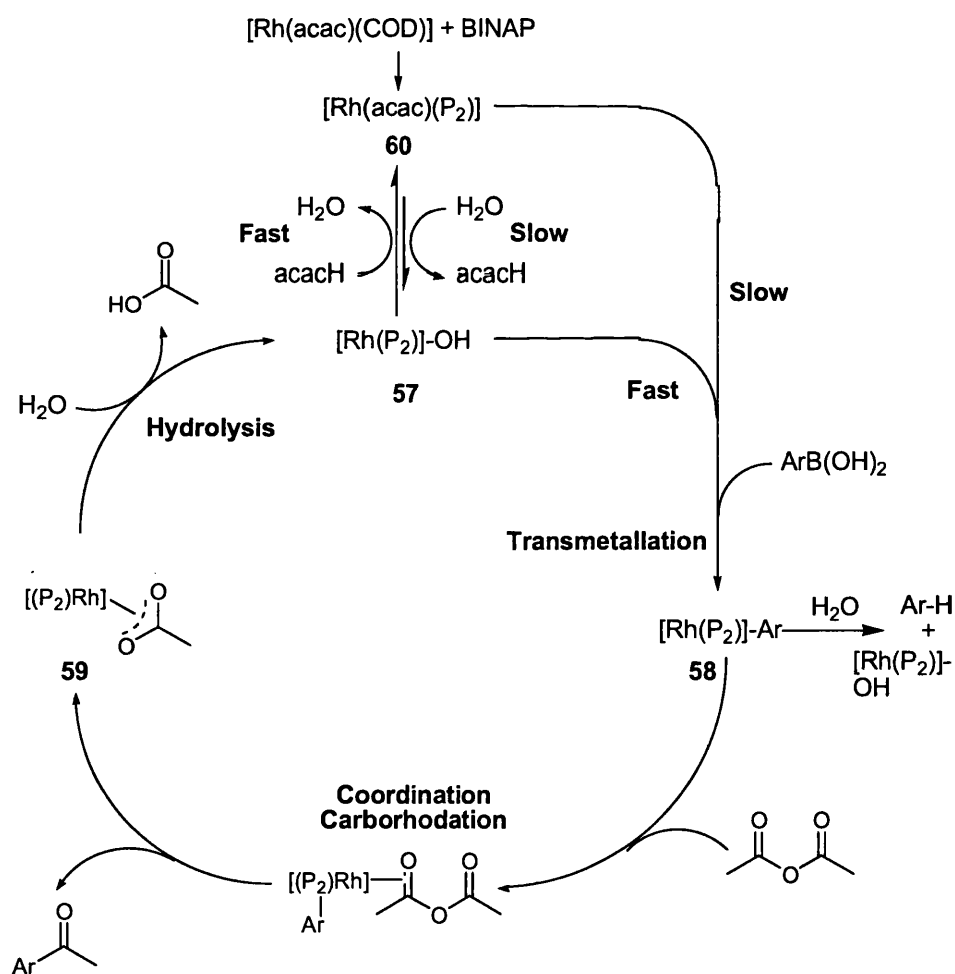
The anticipated reaction involves the addition of an arylboronic acid to an activated acyl group, such as an anhydride, in the presence of a rhodium catalyst to form an aromatic ketone.



Scheme 66

It was reasoned that the anhydride will coordinate to rhodium via the π -electrons of the carbonyl allowing the coupling of the aryl group to the anhydride in a 1,2-addition fashion, expelling the desired arylketone and forming a rhodium carboxylate with the corresponding acid. This protocol is based on Hayashi's proposed mechanism for the rhodium catalysed 1,4-addition of arylboronic acid to enones (see Literature Review 1.3).³² The three main stages of this mechanism will comprise of -

1. transmetallation of an aryl group from boron to rhodium **58**.
2. insertion of carbonyl into the aryl-rhodium bond expelling the desired product and forming the rhodium enolate **59**
3. hydrolysis giving the corresponding acid and hydroxorhodium species **57**.

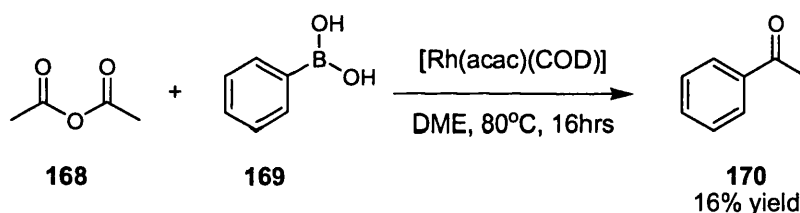


Scheme 67

Many organoboron compounds are air sensitive, and in some cases pyrophoric, while those containing boron-hydrogen, boron-nitrogen, boron-halogen, and to a lesser extent, boron-oxygen bonds, are easily hydrolysed. Boronic acids in contrast are usually crystalline solids that are stable to both air and moisture. They are also of relatively low toxicity (phenylboronic acid LD₅₀ oral-rat = 740mg/kg) and environmental impact. Furthermore, they offer advantages over organolithium, organomagnesium or other organometallic reagents due to their tolerance to a wide variety of functional groups.³⁷

2.4 RHODIUM CATALYSED ADDITION OF BORONIC ACIDS TO ANHYDRIDES

2.4.1 Preliminary Studies

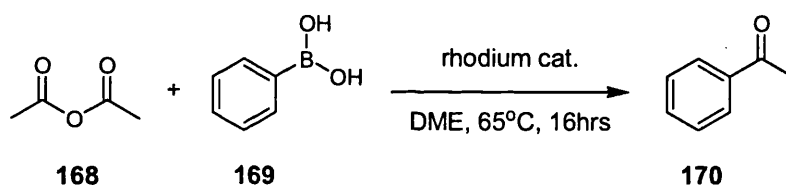


Scheme 68

To assess the reactivity of phenylboronic acid **169** to acetic anhydride **168**, 5mol% of [Rh(acac)(COD)] was added to a solution of phenylboronic acid (1.6equiv.) and acetic anhydride (1equiv.) in DME and stirred for 16 hours at 80°C (Scheme 68). These conditions were first published by Miyaura for the 1,4-addition of arylboronic acids to enones however in our reaction these conditions produced only a 16% yield of acetophenone **170**.^{8,74-77} Whilst this was disappointingly low, the observed formation of acetophenone was encouraging as it was indicative of an effective protocol for ketone synthesis.

2.4.2 Catalyst Development

A wide variety of rhodium catalysts are used in 1,4-addition reactions however there is a trend towards $[\text{Rh}(\text{acac})]$ based catalysts being more reactive in additions to activated olefins.³⁷ This is due to the $[\text{Rh}(\text{acac})(\text{BINAP})]$ catalyst forming the more active $[\text{Rh}(\text{OH})(\text{BINAP})]_2$.³² This catalyst is much more efficient at transmetallation which can even be achieved at room temperature. $[\text{Rh}(\text{BINAP})\text{Cl}]_2$ however does not form this catalyst and requires the addition of potassium hydroxide to do so. As the addition to anhydrides also involves the transmetallation of the aryl group from boron to rhodium, it was postulated that $[\text{Rh}(\text{acac})]$ based catalysts should perform well. Therefore, the activity of these and a variety of other catalysts were examined for this procedure.



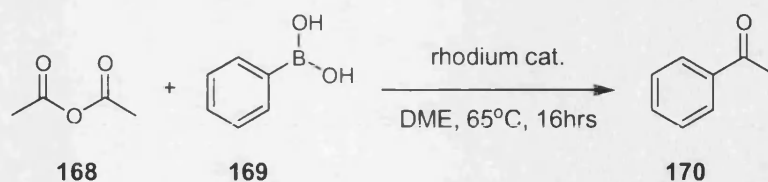
Scheme 69

It is important to first note that in the absence of catalyst no reaction takes place.

Three different $[\text{Rh}(\text{acac})]$ core catalysts were investigated in the absence of phosphine ligands (Table 1). Unfortunately the highest yield observed was a disappointingly low 27% with $[\text{Rh}(\text{acac})(\text{nbd})]$, and interestingly $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$ proved completely unreactive. However, when the acac ligand is replaced with chloride (e.g. $[\text{Rh}(\text{COD})\text{Cl}]_2$) there was a marked increase in yield in all cases except $[\text{Rh}(\text{nbd})\text{Cl}]_2$. This result is the opposite from previously noted trends and is most strongly seen in the case of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ which gave an 87% yield. To complete the range of rhodium catalysts tested $\text{RhCl}_3 \cdot \text{H}_2\text{O}$, $[\text{Rh}(\text{OAc})_2]_2 \cdot \text{H}_2\text{O}$ and $[\text{Rh}(\text{CF}_3\text{CO}_2)_2]_2$ were all examined but only $[\text{Rh}(\text{CF}_3\text{CO}_2)_2]_2$ was reactive, but only gave a small yield of 34%.

To assess whether the presence of a phosphine ligand would improve the activity of the catalyst, $[\text{Rh}(\text{BINAP})\text{Cl}]_2$ was created *in situ* from $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ and two

equivalents of rac-BINAP. Surprisingly the yield dropped, although only slightly to 83%, leading us to believe that $[\text{Rh}(\text{BINAP})\text{Cl}]_2$ is of similar reactivity to $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ in this case.



Entry ^a	Catalyst	Yield % ^b
1	-	0
2	$[\text{Rh}(\text{acac})(\text{nbd})]$	27
3	$[\text{RhCl}(\text{nbd})]_2$	20
4	$[\text{Rh}(\text{acac})(\text{COD})]$	16
5	$[\text{Rh}(\text{COD})\text{Cl}]_2$	57
6	$[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$	87
7	$[\text{Rh}(\text{C}_2\text{H}_4)_2(\text{acac})]$	0
8 ^c	$[\text{Rh}(\text{BINAP})\text{Cl}]_2$	83
9	$[\text{Rh}(\text{OAc})_2]_2 \cdot \text{H}_2\text{O}$	0
10	$\text{Rh}(\text{CF}_3\text{CO}_2)_2]_2$	34
11	$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$	0

^a Typical reaction conditions: rhodium catalyst (0.006mmol, 1.5mol%), DME (4ml), phenylboronic acid (0.56mmol) acetic anhydride (0.4mmol), 16hours at 65°C.

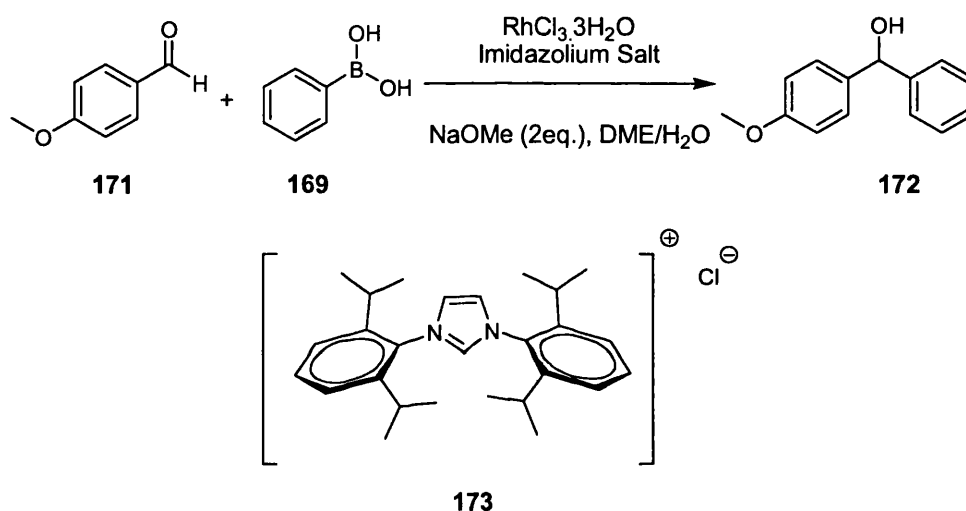
^b isolated yield after flash chromatography.

^c generated in situ from $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ and BINAP.

Table 1

N-Heterocyclic carbenes (NHCs) constitute a class of ligands that exhibit pronounced σ -donor properties but are very poor π -donors. They are easily generated from the corresponding imidazolium salts and have been employed with considerable success in various catalytic transformations involving the turnover of an electron rich transition metal intermediate. In particular, their use has tended towards olefin metathesis and palladium catalysed cross coupling reactions.

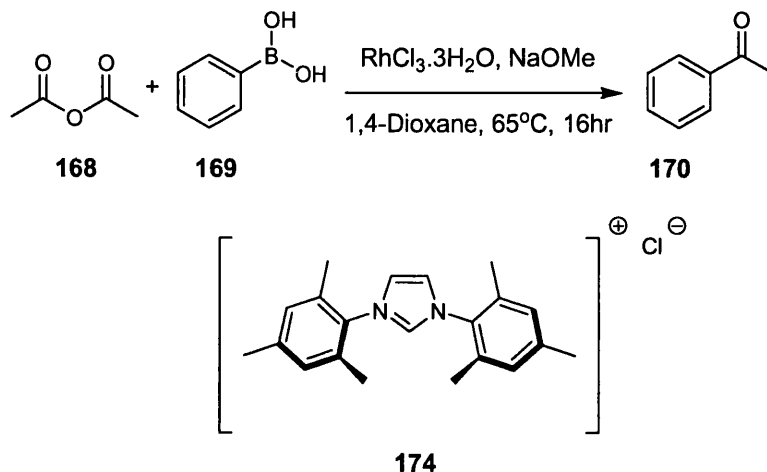
Furstner⁷⁸ utilised these ligands when he demonstrated the rhodium-catalysed addition of organoboron compounds to aldehydes carried out in the presence of the sterically hindered imidazolium salt **173** (Scheme 70).



Scheme 70

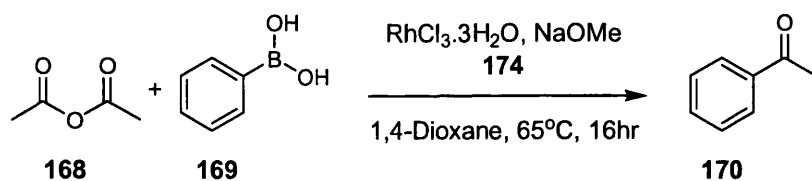
This research showed that the reaction could proceed with the NHC being formed *in situ* from the imidazolium salt with a strong base. Phenylboronic acid was added to *para*-methoxybenzaldehyde **171** in the presence of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$, NHC **173** and sodium methoxide to produce **172** (Scheme 70). The scope of the reaction proved wide-ranging, and chemoselectivity of aldehydes over keto groups was demonstrated. Electron-rich and electron-poor aromatic aldehydes react with similar ease and even sterically hindered aliphatic aldehydes reacted well. However, limitations were observed when applying arylboronic acid derivatives bearing strongly electron-withdrawing groups. Thus, the attempted addition of *para*-nitro or

para-cyanophenylboronic acid to benzaldehyde by means of the present catalyst system proved unsuccessful. This failure is ascribed to the reduced nucleophilicity of these compounds, which makes the transmetalation to the rhodium catalyst unfavourable.



Scheme 71

Given that $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ is one of the cheaper rhodium salts it was decided to explore its application to our methodology for ketone synthesis (Scheme 71). Initial results were promising with a 56% yield after only 30 minutes (Table 2). However, this rate of reaction was not maintained as only an increase of 8% yield was achieved in the next 1.5 hours. These conditions were then unable to compete with $[\text{Rh}(\text{C}_2\text{H}_4)\text{Cl}]_2$ which generated a yield of 86% in 16 hours and so this route was not pursued any further.



Entry ^a	Time	Yield % ^b
1	30mins	56
2	2hrs	64
3	24hrs	82

a Typical reaction conditions: $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$, carbene ligand (3mol%), NaOMe (2 equiv.), 1,4-dioxane (4ml), phenylboronic acid (0.56mmol), acetic anhydride (0.4mmol), 16 hours at 65°C.

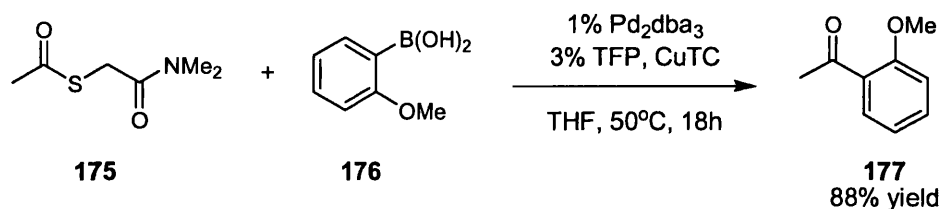
b isolated yield after flash chromatography.

Table 2

2.4.3 Different Acyl Sources

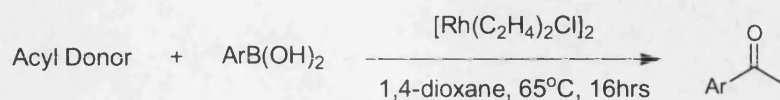
The results of the reaction of boronic acids and acetic anhydride confirmed the feasibility of rhodium-catalysed acylation reactions. To improve the versatility of the process, a range of different acyl sources were explored.

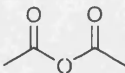

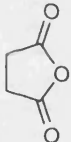
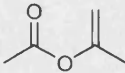
One such possible acyl source is a thiol ester. This has already been applied to the synthesis of simple ketones by Liebeskind.⁷⁹ Coupling of thiol ester **175** with boronic acid **176** in the presence of Pd_2dba_3 /TFP and copper (I) thiophene-2-carboxylate (CuTC) in strictly nonbasic conditions produced ketone **177** in 88% yield (Scheme 72).



Scheme 72

Although yields obtained were generally high, this reaction is not ideal as thiol esters are toxic. It was also professed that mixed anhydrides were not intermediates in this reaction with the thiol esters not reacting with CuTC either alone or in the presence of the palladium catalyst. Due to this report thiol esters will not be included in this investigation. However, acid chlorides, isoprenyl acetates and cyclic anhydrides were included in the substrates to be examined.



Entry ^a	Starting Material	Yield (%) ^b
1		87
2		0
3		0
4		32

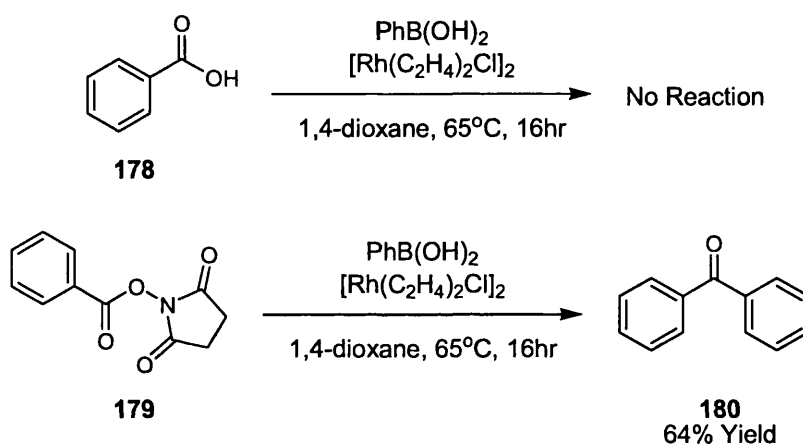
a Typical reaction conditions: $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (0.006mmol, 3mol%), 1,4-dioxane (4ml), boronic acid (0.56mmol) starting material (0.4mmol), 16 hours 65°C .

b isolated yield after flash chromatography.

Table 3

Unfortunately when studied, both the acid chloride and the cyclic anhydride did not provide any product; isoprenyl acetate also gave a disappointingly low 32% yield (Table 3). This maybe due in part to the fact that they are less able to coordinate to the rhodium leading to an inability to form the activated acyl group especially in the

case of the cyclic anhydride. By re-examining the proposed mechanism (section 2.2) it can be seen that a second carbonyl group needs to be available to coordinate to the rhodium to form the rhodium enolate. This cannot be formed for acyl chloride and is unavailable due to steric hindrance with the cyclic anhydride. However the isoprenyl acetate shows some activity as the alkene group can coordinate. Also the presence of the chloride group will affect the electronics and dipole of the carbonyl double bond rendering it even less likely to coordinate.



Scheme 73

Due to the large number of carboxylic acids available the direct coupling of these with boronic acids would be very attractive. Unfortunately the reaction of carboxylic acid **178** failed to yield any product (Scheme 73). This led to the consideration of *N*-hydroxysuccinimide (NHS) esters of the carboxylic acids such as **179** which can be easily formed through the use of coupling reagents such as DCC. This proved successful with **179** furnishing a 64% yield of benzophenone (**180**). This offers a feasible alternative to the anhydride, should anhydride formation prove elusive or too costly.

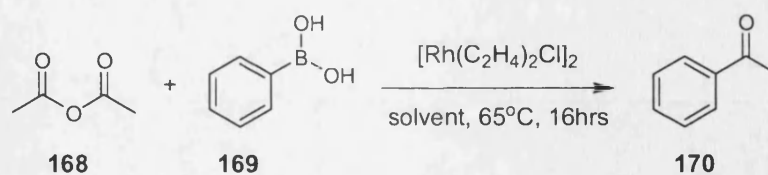
2.4.4 Optimisation

To investigate whether the yield could be increased further a number of parameters were explored.

Solvent Study

Changing the solvent the reaction is performed in can alter the solubility of the reagents, as well as any catalyst intermediates. Thus an investigation of a range of solvents reacted at a variety of temperatures, in an attempt to avoid harsh reflux conditions, was performed (Table 4).

Two clear contenders were immediately apparent, DME and dioxane both proving very effective with yields of 85% and 83% respectively. Reaction of phenylboronic acid with acetic anhydride in a solution of DME/water (6/1) generated an 84% yield of acetophenone illustrating that the reaction is unaffected by water. Despite the comparable yield, DME/water was rejected as the solvent system of choice as the presence of too much water increases the hydrolysis of boronic acids, which could lead to a reduction in yield when more sensitive boronic acids are utilised. However this result was very useful as it indicated that the preferred solvent would not have to be rigorously dried. Dioxane was selected as the preferred solvent as its boiling point is higher thus enabling the reaction temperature to be raised for less reactive substrates without the need to resort to reflux conditions.



Entry ^a	Solvent	Temperature	Yield % ^b
1	DME	65	85
2	THF	65	37
3	Dioxane	100	83
4	Toluene	100	17
5	1-(Trifluoromethyl)Benzene	100	35
6	DME/water (6/1)	65	84

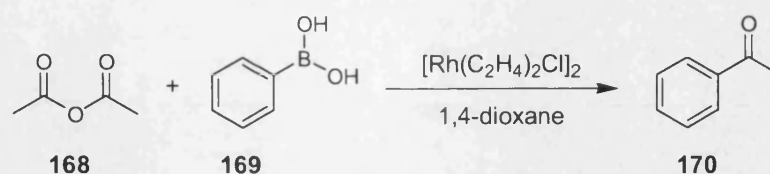
a Typical reaction conditions: $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (0.006mmol, 1.5mol%), solvent (4ml), phenylboronic acid (0.56mmol) acetic anhydride (0.4mmol), 16 hours.

b isolated yield after flash chromatography.

Table 4

Time & Temperature Study

By elevating both the temperature and elongating the reaction times it can be seen that generally the yields increase. Thus, a study was performed investigating the effects of changing the reaction times at various temperatures (Table 5).



Entry ^a	Temperature °C	Time h	Yield % ^b
1	21	2	26
2	21	6	54
3	21	24	65
4	65	2	38
5	65	6	78
6	65	24	89
7	100	2	64
8	100	6	87
9	100	24	83

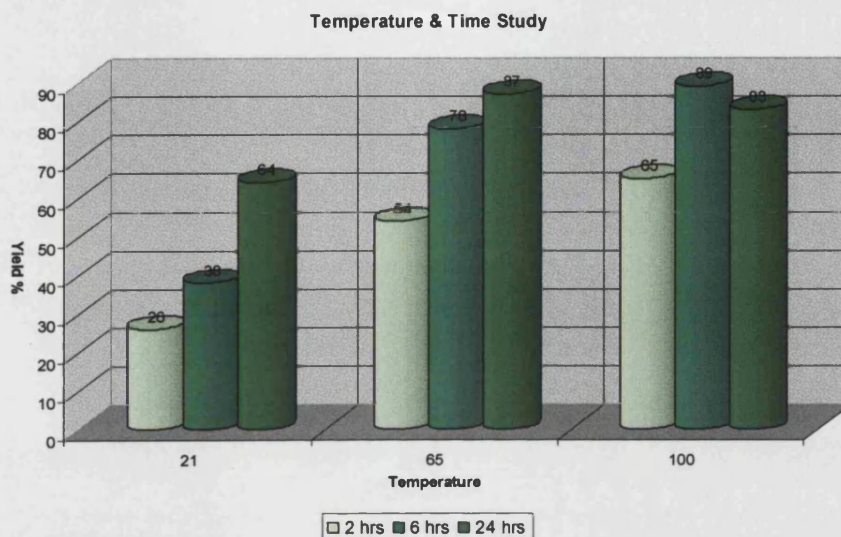
a Typical reaction conditions: $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (0.006mmol, 1.5mol%), 1,4-dioxane (4ml), phenylboronic acid (0.56mmol) acetic anhydride (0.4mmol).

b isolated yield after flash chromatography.

Table 5

When the temperature is raised from room temperature to 100 °C there is an increase in yield after 2 hours from 26% to 64% yield. Also at 65 °C the reaction gave only a 38% yield after 2 hours but increased to 89% after 24 hours. However on closer inspection it can be seen that there is a small reduction of yield in both cases. This is due to the increased prominence of side reactions and their products. These not only manifested themselves in slightly lower yields, but complicated the work up and purification stages. This effect was most pronounced when the reaction was

performed at 100°C where a *reduction* of yield between 6 hours and 24 hours is observed (Graph 1).

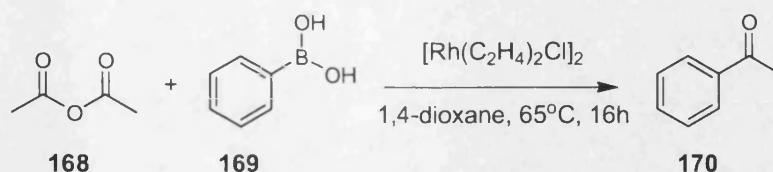


Graph 1

Catalyst Loading Study

The study of the optimal catalyst loading proved once again that there is a fine balance in this reaction between the acceleration of the desired reaction and the production of unwanted side products. Although none of these side products were isolated they are likely to include benzene through hydrolysis of the boronic acid.

It is pleasing to note that a 33% yield can be achieved with catalyst loadings of as low as 0.1mol%. However, there is a decrease of 15% yield when the loading is increased from 3mol% to 5mol%. Thus, 3mol% is the optimum catalyst loading for a 16 hour reaction at 65 °C (Table 6).



Entry ^a	Catalyst Loading	Yield (%) ^b
1	0.1	33
2	0.5	42
3	1	56
4	3	87
5	5	72

a Typical reaction conditions: $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ catalyst, 1,4-dioxane (4ml), phenylboronic acid (0.56mmol), acetic anhydride (0.4mmol), 16hours at 65°C .

b isolated yield after flash chromatography.

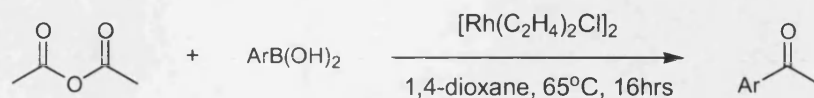
Table 6

2.5 SCOPE OF REACTION

2.5.1 Range of Boronic Acids

Under these optimised conditions a wide range of boronic acids were examined (Table 7). It was useful to observe that although electronic effects may reduce the rate of the reaction, the composition of the product was unaffected by the nature and position of the substituent on the boronic acid. This versatility is in contrast to trends seen in Friedel Crafts acylation reactions, where the presence of deactivating groups such as a nitro group demonstrated a dramatic reduction in yield. Under the rhodium-catalysed system we observed only a modest reduction to 56% (entry 2) compared to 87% (entry 1). It should also be noted that the positioning of such groups does not influence the yield; the methoxy group (normally *ortho*, *para*

directing in Friedel Crafts) presents reasonable yields in both the *para* and *meta* positions with 67% (entry 4) and 69% (entry 5) yields respectively. Of particular note is the use of *trans*-2-vinylphenylboronic acid (entry 8) which not only reveals the ability of alkenylboronic acids to participate in the reaction but demonstrates the selectivity of these conditions in providing only acylation products rather than going further to the 1,4-addition products.



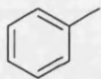
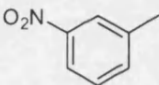
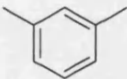
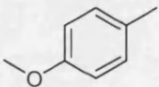
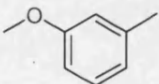
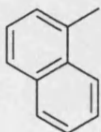
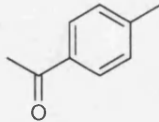
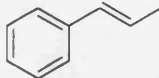
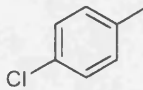
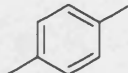
Entry ^a	Ar	Product	Yield % ^b
1		170	87
2		181	56
3		182	68
4		183	67
5		184	69
6		185	76

Table 7 (continued overleaf)

Entry ^a	Ar	Product	Yield % ^b
7		186	86
8		187	54
9		188	62
10		189	78

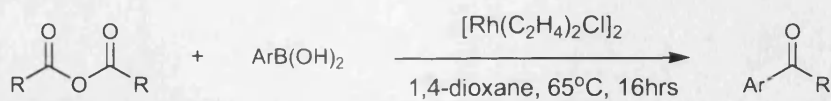
a Typical reaction conditions: $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (0.006mmol, 3mol%), 1,4-dioxane (4ml), boronic acid (0.56mmol), acetic anhydride (1ml of 0.4M solution), 16 hours, 65°C.

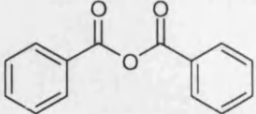

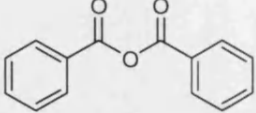
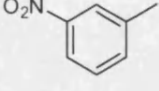
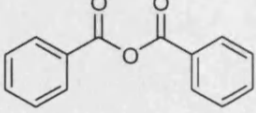
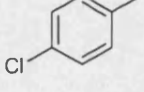
b isolated yield after flash chromatography.

Table 7

2.5.2 Range of Anhydrides

To further demonstrate the scope of the methodology, the reaction of benzoic anhydride was studied (Table 8). All organoboronic acids exhibited moderate yields and similar traits were found with the deactivated aromatic, 4-chlorophenyl, achieving a good yield of 63% (Table 8, entries 3). The highest yield was achieved when utilising phenylboronic acid with an excellent 76% yield (entry 1).



Entry ^a	Anhydride	Ar	Product	Yield % ^b
1			180	76
2			190	59
3			191	63

a Typical reaction conditions: $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (0.006mmol, 3mol%), 1,4-dioxane (4ml), boronic acid (0.56mmol) benzoic anhydride (0.4mmol), 16 hours 65°C.

b isolated yield after flash chromatography.

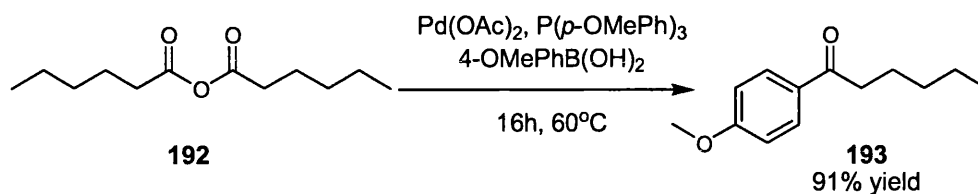
Table 8

Mixed Anhydrides

During our investigation Gooßen^{80, 81} and co-workers developed a system whereby carboxylic acids are transformed into ketones. Since most carboxylic acids can easily be converted into anhydrides this would be done *in situ* allowing the coupling reaction to take place.

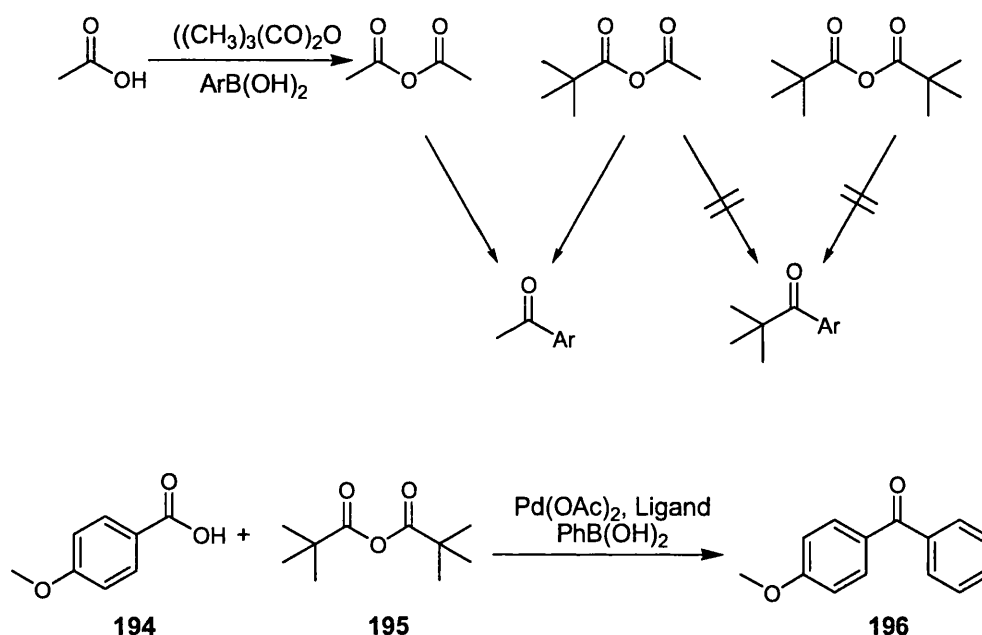
They first demonstrated the feasibility of the coupling of anhydrides and boronic acids in the presence of a palladium catalyst. Hexanoic anhydride **192** (1mmol) reacted with 4-methoxyphenylboronic acid (1.2mmol) in the presence of palladium (II) acetate (0.03mmol) and tri-*p*-methoxyphenylphosphine (0.07mmol). This produced a 91% yield of aromatic ketone **193** (Scheme 74). These conditions were generally successful for a variety of both anhydrides and boronic acids. However, for the best results different phosphine ligands are required depending on the steric

and electronic properties of the anhydrides. For example, for more electron-poor aryl derivatives triphenylphosphine or diphenylferrocenylphosphane are more effective.



Scheme 74

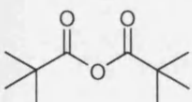

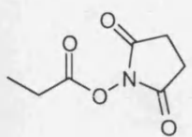

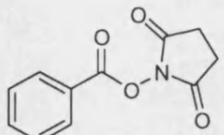

Although the majority of anhydrides reacted well, pivalic anhydride proved too hindered to react at all. This opened up the opportunity for achieving an *in situ* activation of sterically less hindered carboxylic acids by generation of the corresponding mixed anhydrides. *Para*-methoxybenzoic acid **194** reacted with phenylboronic acid in the presence of pivalic anhydride **195** and palladium(II) acetate/ligand to produce only *para*-methoxybenzophenone **189** in 55% yield (Scheme 75). The amount of water present in the reaction proved crucial. In the absence of water less than 1% of the ketone was formed, with two equivalents the reaction almost reaches completion. However, with ten equivalents this drops to around 80% yield.



Scheme 75

It was pleasing to note that when pivalic anhydride was applied under our conditions it did react with phenylboronic acid to furnish a 28% yield of ketone **197** (Table 9). Although this is a low yield it does show that even the most sterically challenging substrates are capable of reacting under these conditions. Unfortunately this negates the ability to form mixed anhydrides from pivalic anhydride and carboxylic acids in the same way that Gooßen accomplished ketone synthesis from carboxylic acids.⁸¹

Fortunately synthesis of ketones from carboxylic acids can be achieved through the initial formation of the *N*-hydroxysuccinimide ester and its subsequent reaction. Both benzophenone and propiophenone were synthesised from phenylboronic acid and the appropriate NHS ester in 64% and 43% (Table 9, entries 3 & 2) respectively. By comparing the yield of the reaction of benzoic anhydride with phenyl boronic acid (76% yield) with that of the reaction of the phenyl NHS ester and phenyl boronic acid (64% yield) it can be seen that the NHS ester is slightly less reactive, but a good yield is still achieved.

Entry ^a	Anhydride	Ar	Product	Yield % ^b
1			197	28
2			198	43
3			180	64

a Typical reaction conditions: $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (0.006mmol, 3mol%), 1,4-dioxane (4ml), phenylboronic acid (0.56mmol) mixed anhydride (0.4mmol), 16 hours 65°C.

b isolated yield after flash chromatography.

Table 9

2.6 CONCLUSION

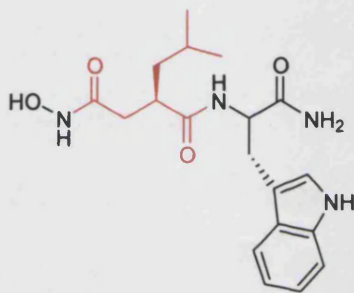
A new and widely applicable methodology for the synthesis of simple ketones has been established. The reaction requires low catalyst loadings and is unaffected by both air and the presence of a reasonable amount of water. It has been shown to be tolerant to a wide variety of functional groups and the yield is almost unaffected by both the position on the aromatic ring and steric bulk of such groups. This method could therefore be applied to complex organic synthesis through either the construction of the anhydride or the formation of the NHS ester.

CHAPTER THREE:
Rhodium-Catalysed Additions To Itaconate Esters

3 RHODIUM-CATALYSED ADDITIONS TO ITACONATE ESTERS

3.1 AIMS AND OBJECTIVES

The object of this project was to explore the 1,4-addition of organoboronic acids to dialkyl itaconate esters, the products of which are synthetically useful as they are important intermediates for the synthesis of many natural products; for example, matrix metalloproteinase inhibitor **199**.⁸²



199

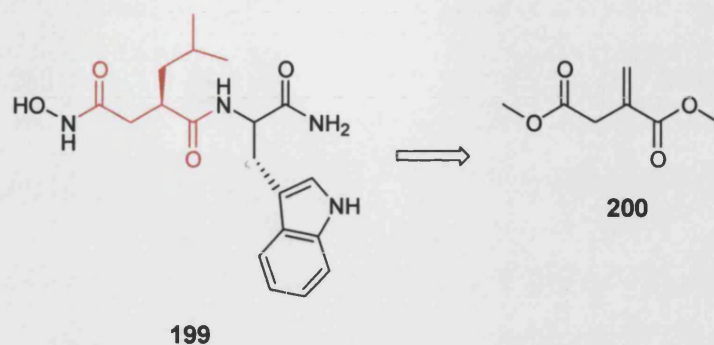
Figure 1

Initial studies will focus on the racemic synthesis of 2-substituted succinic esters, through the study of a range of rhodium complexes and conditions. It was felt that aqueous conditions would be optimum for environmental reasons as well as suitability towards a range of functional groups. Once optimal conditions have been established, a series of 2-substituted succinic esters will be prepared from a range of boronic acids and a select group of dialkyl itaconate esters.

Once a route to racemic products has been identified, focus will be switched to developing an asymmetric version of this reaction. This will entail an investigation of key reaction parameters including a variety of rhodium salts, enantiopure ligands, organoboranes and additives. After a thorough optimisation a range of 2-substituted succinic esters will be prepared in both (*R*)- and (*S*)-configurations.

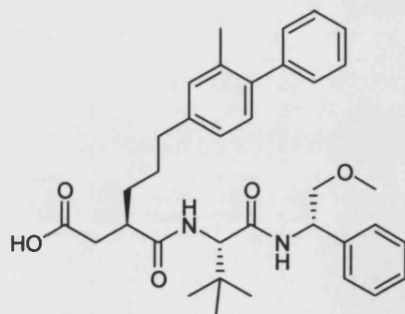
3.2 BACKGROUND

The synthetic usefulness of 2-substituted succinic esters can be demonstrated by looking at the synthesis of three major drugs, MMP inhibitors, lignan lactones and CNS drugs.



Scheme 76

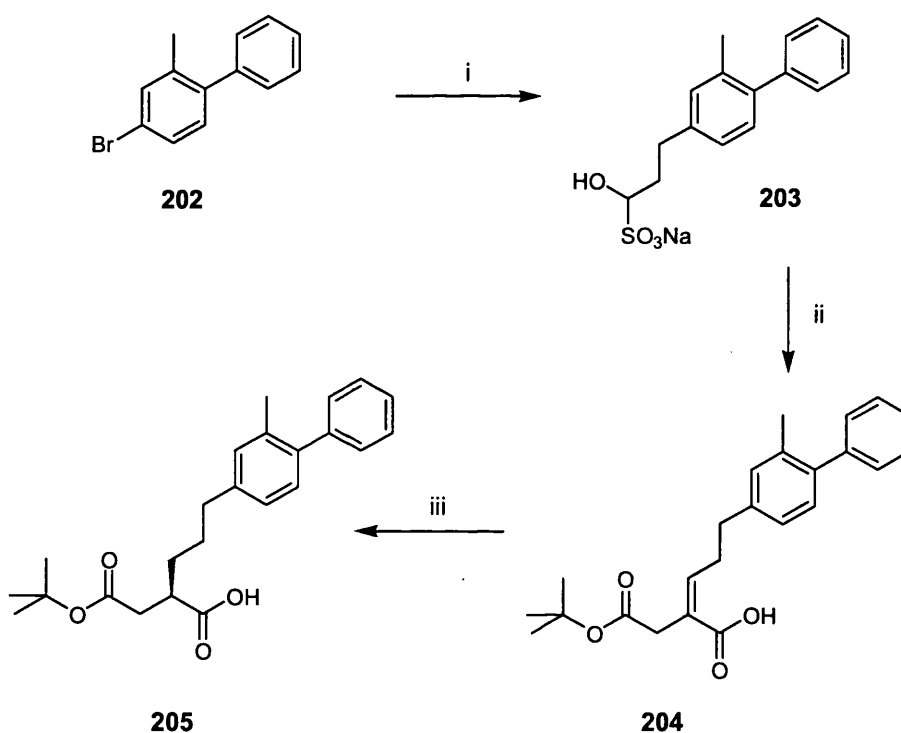
Matrix metalloproteinases (MMP's) are a group of enzymes involved in the repair, degradation, and remodelling of extracellular matrix proteins in tissues. Since they have a destructive potential, failure to regulate MMP activity in physiological processes may lead to such problems as tissue destruction, and diabetic ulcers.⁸² UK-370, 106, 201, a potent and selective MMP-3 inhibitor discovered by chemists at Pfizer,⁸³ has been developed as a candidate to treat pathological conditions, involving tissue destruction.



UK-370, 106 201

Figure 2

In the initial medicinal chemistry route 2-alkyl succinate derivative **205** (an intermediate within the synthesis of UK-307, 106) was prepared in six steps. Thomson *et al.*⁸⁴ later reduced this to three steps through the use of an asymmetric hydrogenation of the alkene of **204** (Scheme 77). Biaryl bromide **202** was reacted with allyl alcohol under Jeffery's conditions to afford biarylpropanal, which was isolated in crystalline form as the sodium metabisulfite form **203**. Phosphonosuccinate was then prepared from triethyl phosphonacetate and isolated in crystalline form. Treatment of the bisulfate and the phosphonosuccinate with an excess of potassium *t*-butoxide, led to *cis*- β -substituted itaconate **204** in around 61% yield. This was followed by ruthenium catalysed asymmetric hydrogenation to produce (*R*)-**205** in a 65% yield and 98% ee.



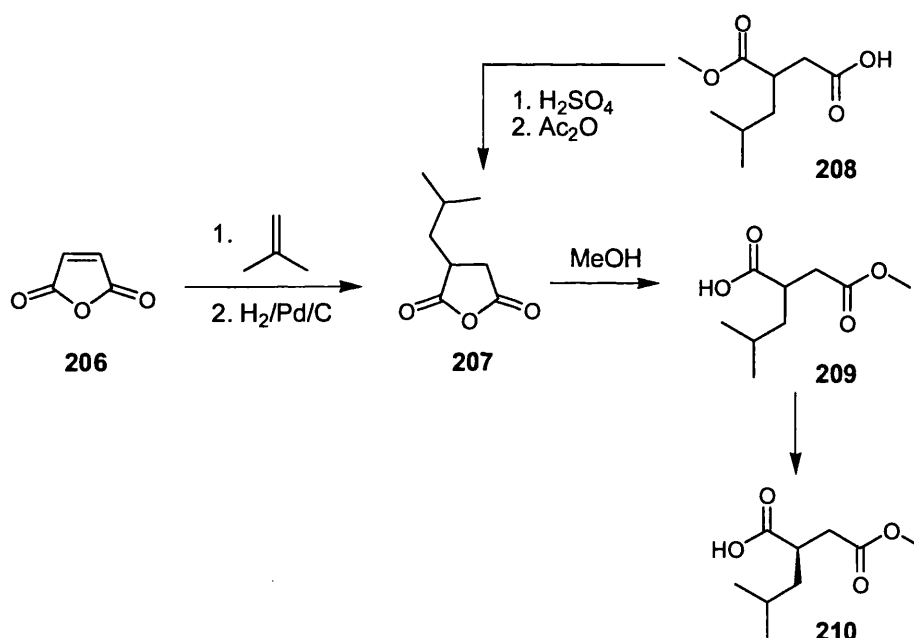
i) allyl alcohol, Pd(OAc)₂, P(*o*-tolyl)₃, Bu₄NCl, NaHCO₃, MeCN, reflux; Na₂S₂O₅, MeOH, H₂O,

ii) *t*-BuOK, 3-(Diethoxyphosphoryl)succinic acid 1-*t*-Buty ester, 0°C; EtOAc, C₆H₁₁NH₂,

iii) [(*S*)-BINAP-Ru-(*p*-cymene)Cl]₂Cl, MeOH, H₂O, H₂ (60psi), 60°C.

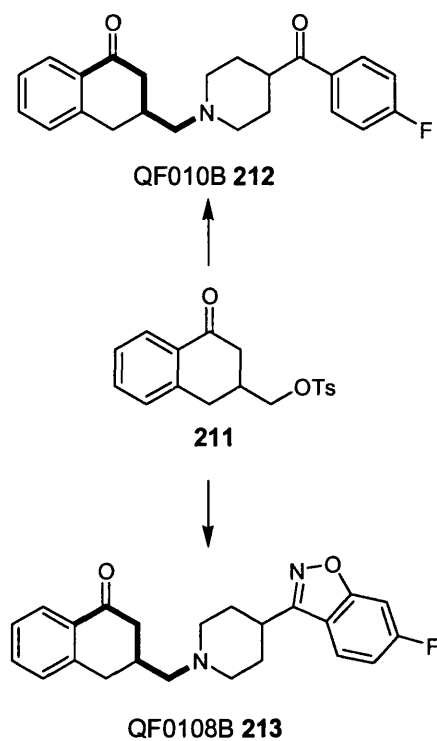
Scheme 77

Levy *et al.*⁸⁵ also synthesised a range of MMP inhibitors in order to establish a connection between the structure and the activity of the compound. To do this they prepared a large quantity of intermediate **210** (Scheme 78). Maleic anhydride **206** was reacted with *iso*-butylene, and the resulting ene-adduct was reduced to **207** via catalytic hydrogenation. Subsequent methanolysis of the anhydride produced the mixture of regioisomers **208** and **209**. Separation and resolution of the desired regioisomer **209** with (*S*)-methylbenzylamine yielded the final product **210**. The undesired regioisomer **208** can be converted back into anhydride **207** via hydrolysis to the diacid followed by dehydration with acetic anhydride.



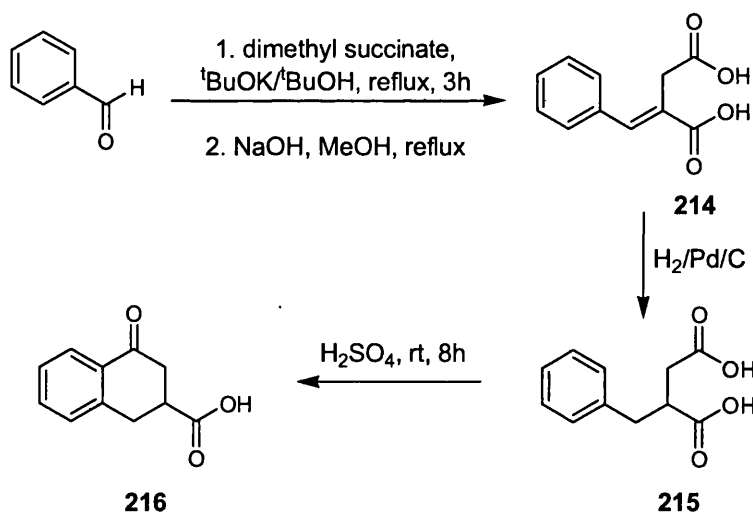
Scheme 78

Succinic acids have also been utilised in the preparation of (*R*)-(-)- and (*S*)-(+)-3-hydroxymethyl-1-tetralone tosylates **211**, intermediates in the synthesis of new CNS drugs **212** and **213** (Scheme 79).



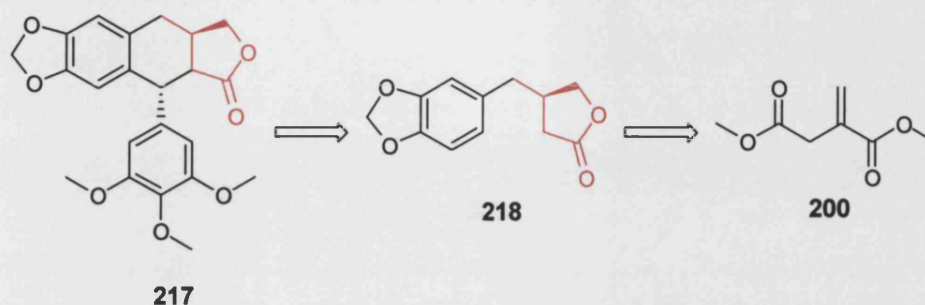
Scheme 79

In this synthesis Raviña *et al.*⁸⁶ produced 2-benzylsuccinic acid in only two steps *via* Stobbe condensation of benzaldehyde with dimethyl succinic acid followed by hydrogenation of the double bond leads to 2-benzylsuccinic acid **215** (Scheme 80). This then forms tetralonecarboxylic acid **216** through cyclisation in the presence of H_2SO_4 in a 50% overall yield.



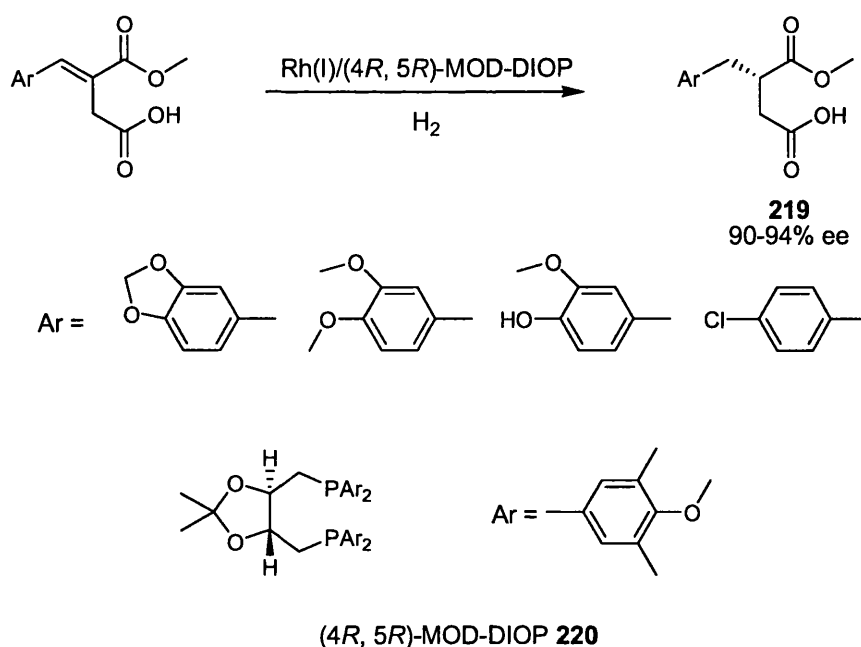
Scheme 80

Lignan lactones such as deoxypodophyllotoxin **217** are known to show cytotoxic activities and can be utilised as anti-cancer drugs. Achiwa *et al.*⁸⁷ synthesised a range of these compounds using the asymmetric form of the above route. A retrosynthesis of which is shown in Scheme 81.



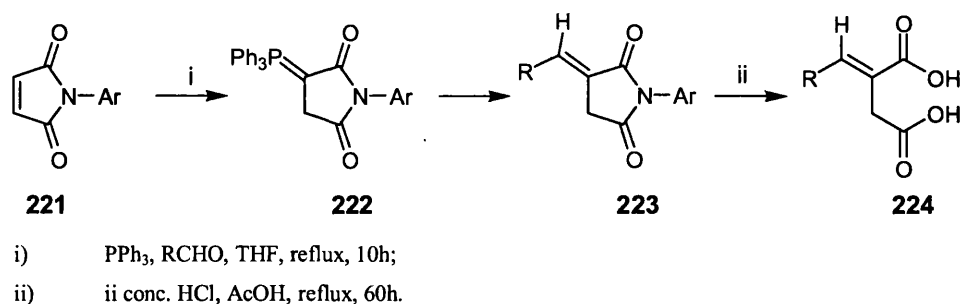
Scheme 81

Stobbe condensation of dimethyl itaconate and the required substituted benzaldehyde was followed by asymmetric hydrogenation of the alkene (Scheme 82). The asymmetric hydrogenation was carried out in methanol at 30°C for 40 hours under 1 atm. of H₂ in the presence of triethylamine using the neutral rhodium complex of (4*S*,5*S*)-MOD-DIOP **220**. This is prepared by mixing [Rh(COD)Cl]₂ and MOD-DIOP in methanol. All reactions gave high optical purity (>93%ee) and quantitative yields. Optically pure (*R*)-arylmethylsuccinic acid monomethyl esters **219** were easily obtained by a single recrystallisation of the products from isopropyl ether.



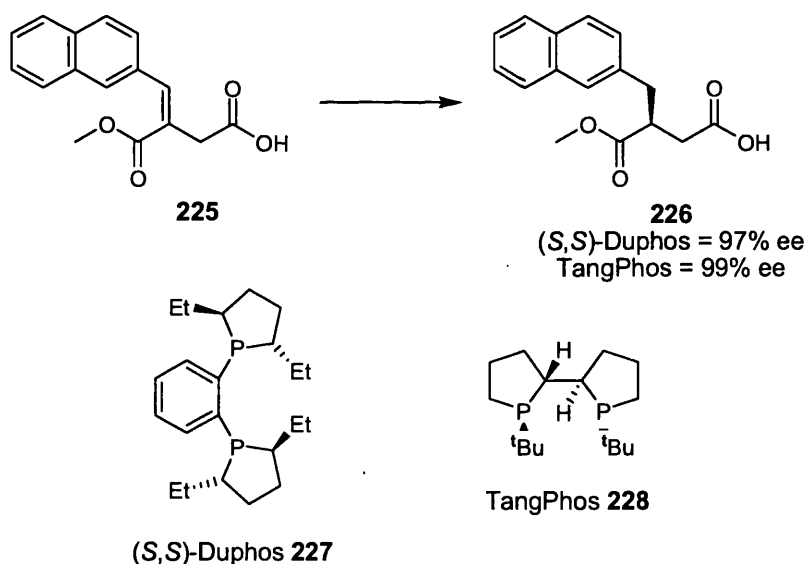
Scheme 82

One of the most common routes to 2-substituted succinic acids involves the synthesis of alkylidene succinic acids followed by metal catalysed hydrogenation. Argade *et al.*⁸⁸ obtained (*E*)-alkylidenesuccinic acids *via* a general two-step synthesis utilizing Wittig methodology (Scheme 83). The reaction of maleimide **221** with triphenylphosphine (TPP) furnished the intermediate Wittig adduct **222**, which *in situ* condensed with aliphatic aldehydes to afford the alkylidenesuccinimides **223** in excellent yields. These afforded the (*E*)-alkylidenesuccinic acids **224** on hydrolysis under reflux in a mixture of concentrated hydrochloric acid and glacial acetic acid (1:1) in quantitative yields.



Scheme 83

Once the (*E*)-alkylidenesuccinic acids have been formed, one of the simplest, and most common, methods for forming the chiral 2-substituted succinic acid is rhodium-catalysed asymmetric hydrogenation. There are many chiral ligands which successfully catalyse the asymmetric hydrogenation of the parent itaconic acid or its methyl ester.⁸⁹⁻⁹⁵ However, it is the hydrogenation of β -substituted itaconic acid derivatives that is of most interest. This normally presents a problem as Stobbe condensation yields a mixture of *E* and *Z* substrates. As these two substrates should show different enantioselectivities with the same ligand, and separation before hydrogenation is very difficult, a low enantioselectivity is often observed. (*S,S*)-Et-Duphos **227** was utilised by Burk *et al.* to complete the hydrogenation of β -itaconate **225** (3:1 *E/Z* ratio) to furnish 2-alkylsuccinate **226** in 97% ee (Scheme 84).⁹⁶ Hydrogenation conditions of 0.03mol% [Rh(COD)(Et-Duphos)][BF₄], 10% NaOMe in methanol with 5.5 bar H₂ yielded a range of 2-alkylsuccinates in 97-99% ee. This was then improved on by the use of chiral ligand TangPhos **228** which also achieved 99% ee and greater for a range of 2-alkylsuccinates.⁹⁷ β -itaconate **225** (3:1 *E/Z* ratio) was hydrogenated in the presence of 0.5mol% [Rh(TangPhos)(nbd)][SbF₆] in THF with 20psi H₂ to furnish 2-alkylsuccinate **226** in a 99% ee.



Scheme 84

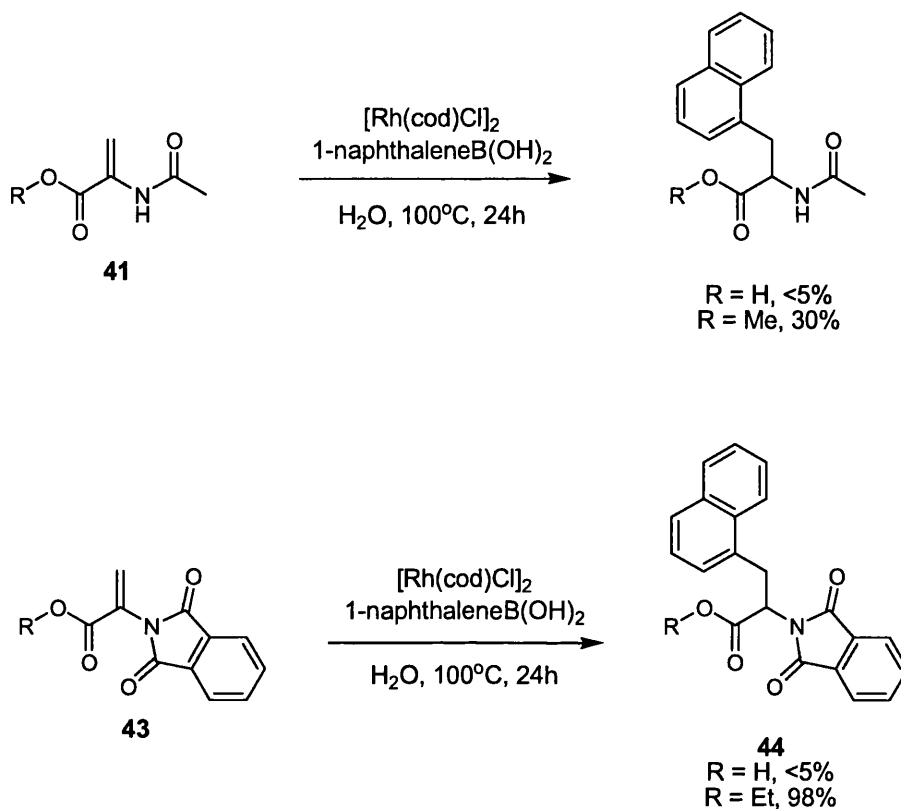
PART A

3.3 AIMS AND OBJECTIVES

The object of this project was to produce a synthetic protocol for the production of 2-substituted succinic esters in one step from dimethyl itaconate ester, which would involve the rhodium-catalysed 1,4-addition of organoboranes.

3.4 BACKGROUND

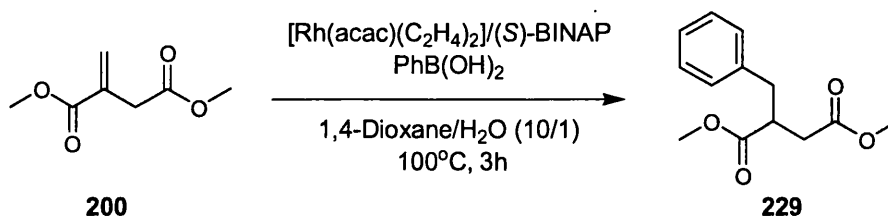
In a previous study the Frost group revealed an efficient rhodium-catalysed conjugate addition of boronic acids to α,β -dehydroamino acid derivatives using only water as a solvent.²⁵ 1-Naphthaleneboronic acid reacted with ethyl α -phthalimidoacrylate **43** in the presence of $[\text{Rh}(\text{COD})\text{Cl}]_2$ in water (Scheme 85). It was remarkable that not only were no other additives required to give a 98% yield, but also the catalytic loading could be reduced to 0.5mol% with no loss in efficiency. It was also observed that not only electron-deficient and electron-rich arylboronic acids were efficient but also that aldehydes did not need protection. This is despite the fact that some rhodium catalysts promote addition reactions to aldehydes. Dehydroalanine derivative **44** was originally used but only gave a 30% yield due to intolerance of the aqueous conditions. This was overcome by the introduction of the phthalimide group, and along with esterification of the free acid group a stable substrate that could undergo 1,4-addition was formed. Both protecting groups can then be cleaved under acidic conditions (6N HCl/AcOH, 4/1) to furnish the unnatural α -amino acid hydrochloride in good yields.



Scheme 85

3.5 RHODIUM CATALYSED ADDITION OF BORONIC ACIDS TO DIMETHYLITAONATE ESTERS.

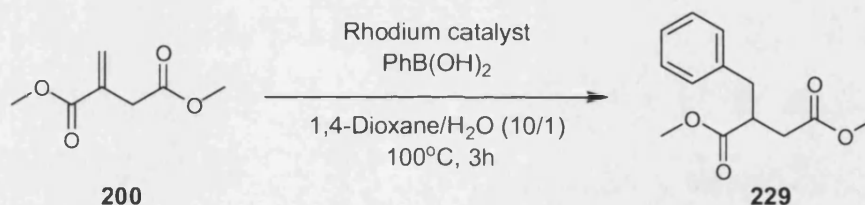
3.5.1 Preliminary Studies



Scheme 86

The reaction was first assessed using Hayashi conditions of $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]/(\text{S})\text{-BINAP}$ in dioxane/water (10/1) at 100°C for 3 hours. This gave a disappointing yield of 26% (Scheme 86). However, once sodium fluoride was added this increased

to a gratifying 72%. Having established the ability of dimethyl itaconate to undergo 1,4-addition with arylboronic acids the investigation turned to examining aqueous conditions. Unfortunately the original aqueous conditions of Frost and Chapman proved inadequate giving an 8% yield.²⁵ These conditions were then tested on a range of rhodium catalysts again to no avail with the highest yield being the 8% observed for $[\text{Rh}(\text{COD})\text{Cl}]_2$, with no yield observed at all for the acac variants. Although there was evidence of some product formed with $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ the yield was too small to enable isolation. Thus whilst these yields are extremely low it has been confirmed that the 1,4 addition of arylboronic acids to dialkyl itaconate esters such as **200** can proceed in water.



Entry	Catalyst	Ligand	Base	Yield % ^c
1 ^a	$[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$	(S)-BINAP	-	26
2 ^a	$[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$	(S)-BINAP	NaF	72
3 ^b	$[\text{Rh}(\text{COD})\text{Cl}]_2$	-	-	8
4 ^b	$[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$	-	-	<5
5 ^b	$[\text{Rh}(\text{acac})(\text{COD})]$	-	-	0
6 ^b	$[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$	-	-	0

a Typical reaction conditions: Dimethyl itaconate, phenylboronic acid (5eq.), rhodium catalyst (5mol%), dioxane/H₂O (10/1), 100°C, 3h.

b Typical reaction conditions: Dimethyl itaconate, phenylboronic acid (2eq.), rhodium catalyst (5mol%), water, 100°C, 24h.

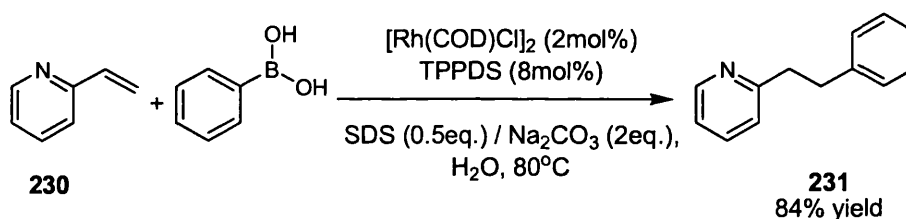
c isolated yield after flash chromatography.

Table 10

3.5.2 The introduction of SDS

During the preliminary investigation it was noted that dimethylitaconate was only sparingly soluble in water even at elevated temperatures. Thus the addition of a phase transfer agent such as sodium dodecyl sulphate (SDS) was considered.

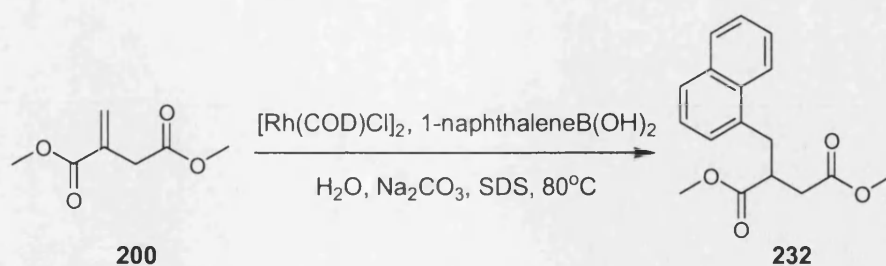
Lautens has already demonstrated that certain heteroaromatic alkenes can undergo 1,4-addition in water.³⁷ The key to this reaction is the addition of the phase transfer agent SDS (Scheme 87). Here 2-vinylpyridine **230** reacted with 2.5 equivalents of phenylboronic acid in the presence of $[\text{Rh}(\text{COD})\text{Cl}]_2$ /TPPDS, Na_2CO_3 and SDS to afford the product **231** in an 84% yield.



Scheme 87

As with Lauten's work, our rhodium-catalysed 1,4-addition benefited from the addition of SDS. 1-Naphthaleneboronic acid reacted with dimethyl itaconate in water in the presence of $[\text{Rh}(\text{COD})\text{Cl}]_2$, Na_2CO_3 and SDS to give a 79% yield of the succinate ester **232** in 16 hours.

The effects of the addition of both SDS and Na_2CO_3 were then explored (Table 11). SDS proved crucial to the reaction even in the presence of two equivalents of Na_2CO_3 if no SDS is added only a 9% yield is observed. It was noted that by increasing the equivalents of SDS the yield improves, but this then levels off after just over half an equivalent when dimethylitaconate is completely solvated at 100°C . The presence of base is also vital for the full potential of the reaction to be achieved. When no Na_2CO_3 is present the yield is almost halved to 55%. This again steadily increases, until it levels at around two equivalents. It is felt that a compromise is reached at two equivalents where the reaction is allowed to continue to its full capability but that the sensitivity of functional groups is not put in jeopardy by creating a very basic environment.



Entry ^a	Na ₂ CO ₃ equiv.	SDS equiv.	Time h	Yield ^b %
1	2	0	16	9
2	2	0.5	16	81
3	2	0.5	4	56
4	2	0.25	4	38
5	2	0.75	4	58
6	2	1	4	57
7 ^c	2	0.5	16	79
8	0	0.5	16	55
9	1	0.5	16	64
10	2	0.5	16	81
11	2.5	0.5	16	85
12	3	0.5	16	80

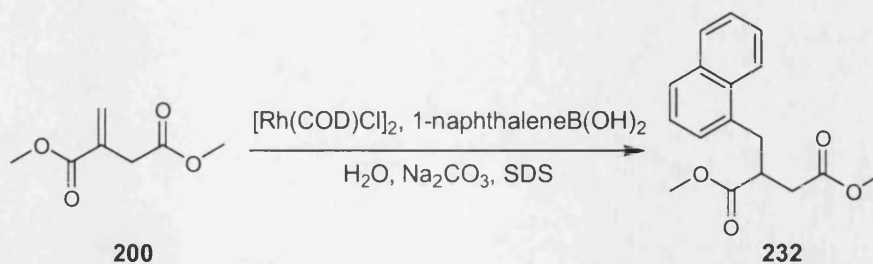
a Typical reaction conditions: Dimethyl itaconate, 1-naphthaleneboronic acid (2eq.), [Rh(COD)Cl]₂ (5mol%), SDS, Na₂CO₃, water, 80°C, 16h.

b isolated yield after flash chromatography.

c SDBS instead of SDS

Table 11

3.5.3 Optimisation of Conditions: Time and Temperature Parameters



Entry ^a	Time h	Temp °C	Yield % ^b
1	2	80	12
2	4	80	49
3	12	80	83
4	16	40	15
5	16	80	81
6	16	110	75

a Typical reaction conditions: Dimethyl itaconate, 1-naphthaleneboronic acid (2eq.), $[\text{Rh}(\text{COD})\text{Cl}]_2$ (5mol%), SDS, Na_2CO_3 , water.

b isolated yield after flash chromatography.

Table 12

It is useful to note that although only a 15% yield of product is obtained at 40°C, the catalytic cycle is still able to proceed at this low temperature (Table 12). Hence, if a substrate was prone to decomposition at higher temperatures, an increased reaction time and a low temperature may be suitable. Generally as the temperature increases, side reactions can occur such as the hydroboration of the boronic acid to the corresponding phenol, so the overall isolated yield decreases. The optimum temperature was deemed to be 80°C where an 81% yield was produced after 16 hours. After 12 hours at this temperature it was shown that the reaction had reached

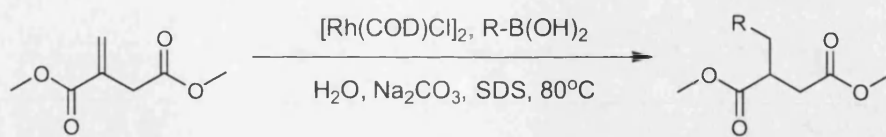
completion. As there was no real decrease in yield between 12 and 16 hours, the most advantageous time for the reaction was set at 16 hours for convenience.

3.6 EXTENDING THE SCOPE

As a range of 2-substituted alkylsuccinic esters would be useful for the synthesis of new derivatives of MMP inhibitors and other drugs, an array of boronic acids were reacted with dimethylitaconate ester (Table 13). This examined the reactions sensitivity towards a range of functional groups as well as their electronic effects and steric constraints.

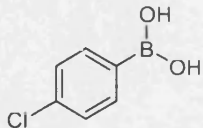
3.6.1 Range of Boronic Acids

It was gratifying to observe that a wide range of boronic acids were successfully applied to this reaction. There was no discrimination between electron-deficient and electron-rich boronic acids and varying of the substitution pattern of the aromatic ring (Table 13, entries 4,5 and 6) demonstrated that steric effects had little consequence on yield. Dimethyl (*para*-methoxyphenyl)succinic ester **234** was produced in a 64% yield and its *meta* substituted counterpart **235** in a 67% yield. It was particularly interesting to note that the highest yield (78%) of the three was obtained at the most sterically challenging point with *ortho*. From a pharmacological point of view the success of the reactions of boronic acids incorporating functional groups such as acyl (-COMe), and nitro (-NO₂) are very important as these groups provide convenient points for further modification. With the lowest yield obtained standing at 56%, this range of boronic acids showed that this reaction could successfully synthesise a large range of 2-substituted succinic esters in one step from commercially available starting materials.



Entry ^a	R-B(OH) ₂	Product	Yield % ^b
1		229	85
2		232	81
3		233	56
4		234	64
5		235	67
6		236	78
7		237	73

Table 13 (continued overleaf)

Entry ^a	R-B(OH) ₂	Product	Yield % ^b
8		238	69

a Typical reaction conditions: Dimethyl itaconate, 1-naphthaleneboronic acid (2eq.), [Rh(COD)Cl]₂ (5mol%), SDS, Na₂CO₃, water.

b isolated yield after flash chromatography.

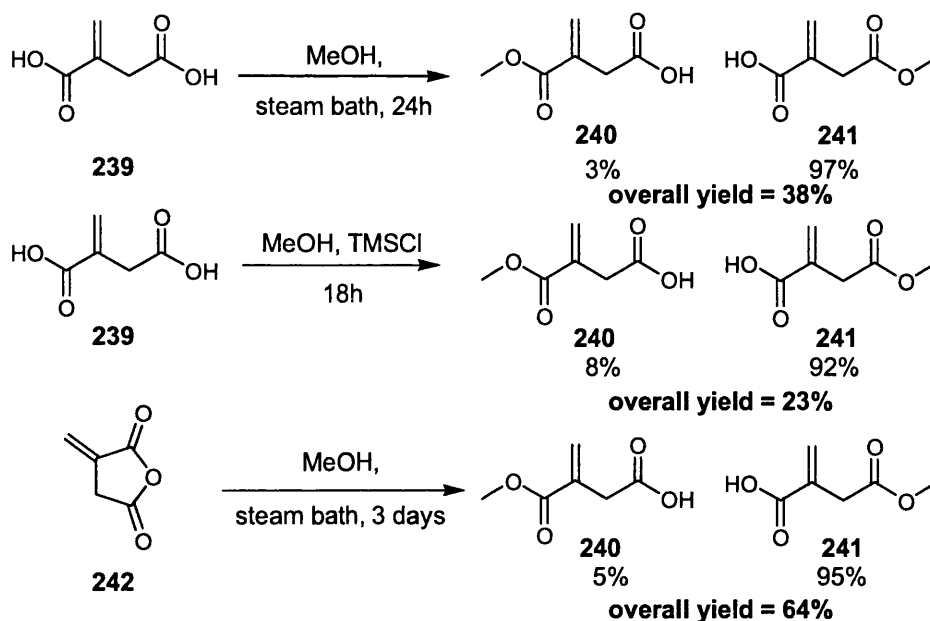
Table 13

The reaction of unsymmetrical esters would be a useful project as if the esters were orthogonally protected, there would be scope for further functionalisation as well as selective cleavage of the esters. This would make the esters and the 1,4 addition of boronic acids to them more attractive for complex synthetic routes.

3.6.2 The preparation of unsymmetrical esters

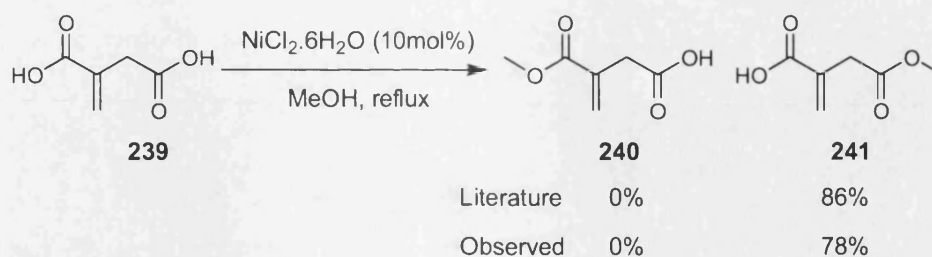
To obtain the unsymmetric esters the first step would be to selectively esterify the non-conjugated acid with an alcohol. It was found that esterification by stirring with the alcohol in question on a steam bath led to very low yield, even after 24 hours (Scheme 88). If the reaction was promoted by the addition of trimethylsilyl chloride, molecular sieves or magnesium sulfate a mixture of the mono and disubstituted products were obtained.

The yield was improved by the use of itaconic anhydride **242**, which was stirred on a steam bath in methanol for 3 days to produce a workable yield of 64% of mixed products. However, the isomers were produced in a 95:5 ratio (non-conjugated ester: conjugated ester), unfortunately the isomers were unseparable at this stage.



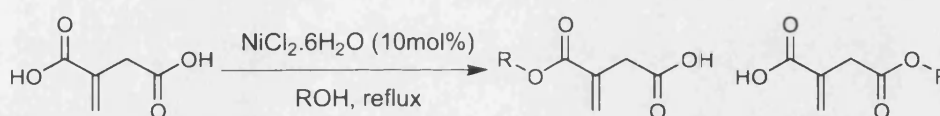
Scheme 88

Ram and Charles developed a very simple and selective esterification for aliphatic carboxylic esters over conjugated or aromatic carboxylic acids (Scheme 89).⁹⁸ The simple experiment involves heating to reflux the carboxylic acid in the alcohol of interest with 10% $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ then extraction with ether or dichloromethane to give pure product in high yields with no need for further purification. The authors put this success down to Ni(II) acting as a mild and selective catalyst due to a suitable balance between its hard and soft acid characters. A range of carboxylic acids were tested and gave high yields for aliphatic carboxylic acids. Mixtures of aliphatic and aromatic acids provided only the esterified aliphatic carboxylic acid products. Finally, itaconic acid was examined and produced a significant 86% non conjugated mono ester and 6% diester with no conjugated monoester detected (Scheme 89). The monosubstituted and disubstituted products were then easily separated in work up.



Scheme 89

This methodology was then exploited to produce two mono non-conjugated esters of itaconic acid (Table 14). Isolation of the desired monoester was performed by washing the aqueous solution with ether to remove any diester. Acidification of the Na_2CO_3 aqueous layer followed by ether extraction furnished the mono esters, which could be used without further purification. Moderate yields of all non-conjugated mono esters were obtained with no traces of their conjugated counterparts.



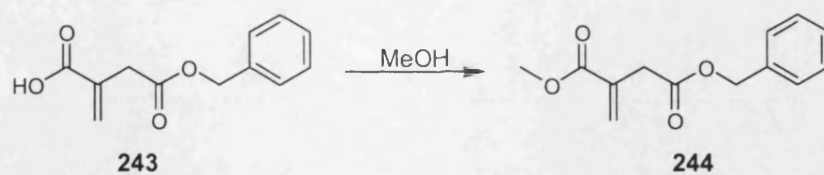
Entry ^a	Alcohol	Time	Yield % ^b
1	Methanol	24	78
2	Benzyl Alcohol	24	69

a Typical Reaction Conditions : Dimethyl itaconate (0.01mol), $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (10mol%), and alcohol (10ml) at reflux.

b Isolated yields.

Table 14

Esterification of the second acid proved problematic as too harsh a method led to degradation of the product. Several esterification processes were tried which finally led to two workable methods (Table 15). EDCI coupling led to a 24% yield and a more gentle acid catalysed esterification led to a 20% yield of **244**. These two alternative methods provide a degree of flexibility as one method maybe more suited to certain alcohols or acids.

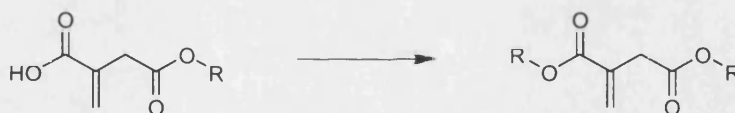


Entry	Conditions	Yield % ^a
1	Steam bath, 3 days	15
2	SOCl ₂ /NEt ₃ , 24h,	0
3	TMSCl, 18h	18
4	Tosic acid, 3 Å molecular sieves, 7 days, 50°C	20
5	EDCI/DMAP/DCM, 20h, room temp.	24

^a Isolated yields.

Table 15

Using the EDCI methodology, two different unsymmetrical esters were obtained in moderate to low yields (Table 16).



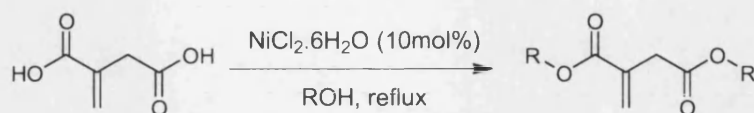
Entry ^a	Starting ester	Alcohol	Yield % ^b
1	<chem>OC(=O)C(=C)CC(=O)OCc1ccccc1</chem>	Methanol	20%
2	<chem>OC(=O)C(=C)CC(=O)OC</chem>	Benzyl alcohol	26%

^a Typical reaction conditions: EDCI (0.51mmol), DCM (10ml), acid (0.51mmol), alcohol (0.255mmol), DMAP (10mol%), 20hours, rt.

^b isolated yields.

Table 16

The three symmetrical diesters of methanol, benzyl alcohol and menthol were synthesised as side products to the original $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ reaction (Table 17). These were produced in low yields but could be made through the same processes as above if greater quantities were required.



Entry ^a	Alcohol	Product	Yield % ^b
1	Methanol	 200	14
2	Benzyl alcohol	 245	16
3	(+)-Menthol	 246	10

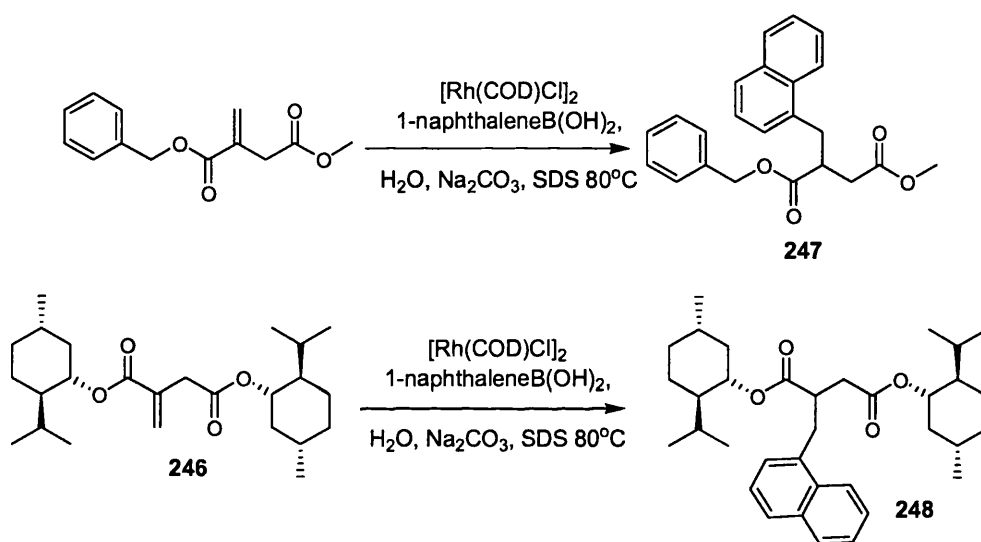
a Typical Reaction Conditions : Dimethyl itaconate (0.01mol), $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (10mol%), and alcohol (10ml) at reflux.

b Isolated yields.

Table 17

3.6.3 1,4 Addition Of 1-Naphthaleneboronic Acids To Esters

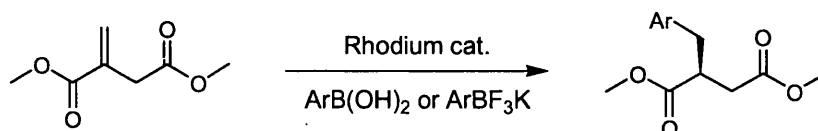
Due to time constraints and only small quantities of each of the unsymmetrical esters and new symmetrical esters being available only two esters were examined in the rhodium-catalysed 1,4-addition reaction. Addition of 1-naphthaleneboronic acid to 1-benzyl-4-methyl 2-methylenesuccinate gave a pleasing 72% yield of addition product **247**, with ester **246** yielding 49% of addition product **248** (Scheme 90). These promising results indicate that the addition of other mixed esters would be viable under these conditions. It should be noted that no evidence of ester cleavage was observed.



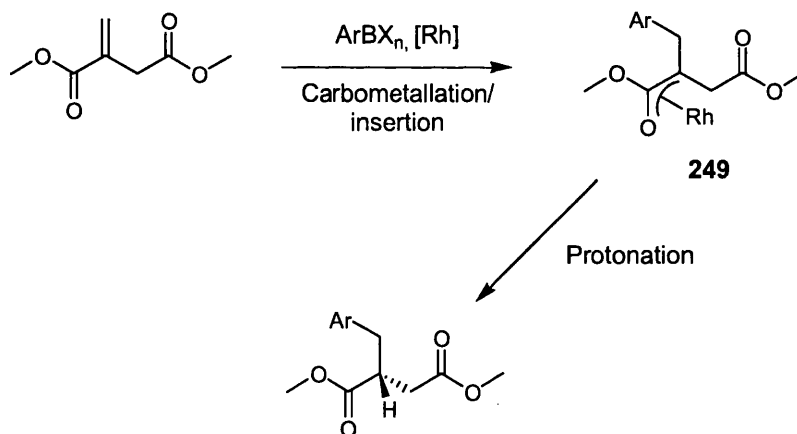
Scheme 90

3.7 CONCLUSION

A novel one step route to 2-alkylsuccinate esters from dialkylitaconate esters has been established. The use of SDS provided the means for the reaction to take place in water thus increased its capabilities in organic synthesis. There is still much more potential for this reaction to be explored but this initial study has shown the method's high tolerance of functional groups and highlighted the possibilities when used in conjunction with unsymmetrical esters.

PART B**3.8 AIMS AND OBJECTIVES****Scheme 91**

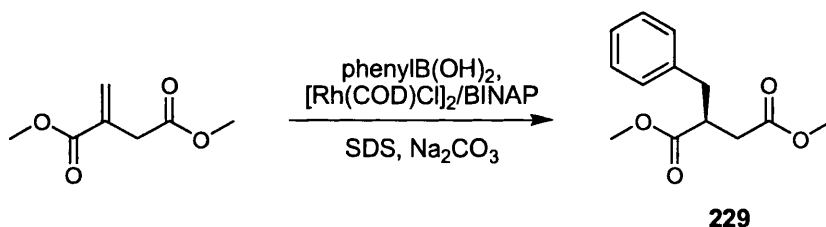
The objective was to synthesis a range of 2-substituted succinic esters through the rhodium catalysed asymmetric 1,4-addition of boronic reagents to itaconate ester derivatives (Scheme 91). Although asymmetric 1,4-additions have been successfully applied to a range of activated alkenes, there are few reports of α -substituted activated alkenes being utilised. This can be attributed to their lower reactivity and crucially, in the asymmetric process, the enantioselectivity is determined at the point of hydrolysis of the oxa- π -allylrhodium intermediate **249** and not at the insertion step (Scheme 92).

**Scheme 92**

3.9 RHODIUM CATALYSED ASYMMETRIC 1,4-ADDITION OF ORGANOBORON REAGENTS TO DIMETHYL ITACONATE

3.9.1 Preliminary Results

Initial experiments focused on the continuation of the previous study of the racemic reaction. Thus phenylboronic acid was added to dimethyl itaconate in a solution of water, SDS and Na₂CO₃ in the presence of [Rh(COD)Cl]₂/(*R*)-BINAP (Scheme 93). This gave **229** in good yield, 65%, however, the enantioselectivity was disappointingly low at 23%ee determined by HPLC analysis. An assay was compiled using a Daicel Chiralcel OD column at ambient temperature and a 98:2 Hexane:IPA solvent system with a flow rate of 1 mL/min. Two clean peaks were found at retention times of 19.0 and 28.9 minutes. The first enantiomer's absolute configuration was determined to be the (*R*)-isomer by comparison with known data for dimethyl 2-benzylsuccinate.

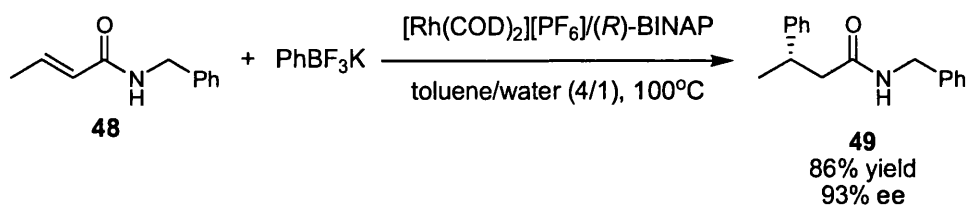


Scheme 93

Hayashi's conditions of 3mol% [Rh(acac)(C₂H₄)₂] and 3.3mol%(*S*)-BINAP in dioxane/H₂O (10/1) solution with phenylboronic acid (5 equiv.) and dimethyl itaconate (1 equiv.) at 100°C for 18 hours also afforded a high yield of 72% of **229**, but again low enantioselectivity (<5% ee).⁹⁹

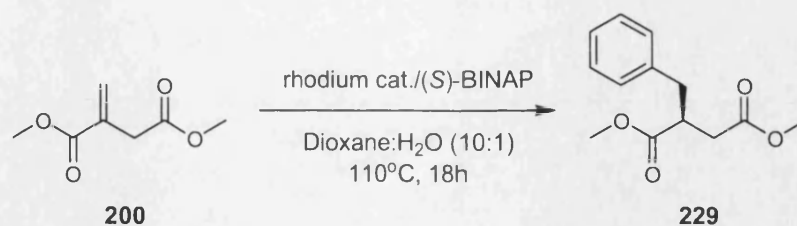
It is known that potassium (organo)trifluoroborate salts offer possible advantages in terms of reactivity and selectivity for many rhodium-catalysed 1,4-addition reactions.^{27,30,100-102} This is exemplified by the addition of potassium trifluoroorganoborates to crotonamides. Potassium phenyltrifluoroborate reacted

with crotonamide **48** in the presence of $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ and (*R*)-BINAP in toluene/water (4/1) at 100°C to furnish **49** in 86% yield and 93% ee (Scheme 94). Genet observed that under these conditions potassium trifluoroborates have fully reacted after 1 hour but boronic acids reached only 62% after 1 hour and 40 minutes. This is thought to be the maximum yield as the remainder of the boronic acid has been used up through protonolysis after transmetallation.



Scheme 94

The selectivity and reactivity of phenylboronic acid compared with commercially available potassium trifluorophenylborate was therefore compared with a range of rhodium catalysts. Both neutral and cationic catalysts were examined with both potassium trifluorophenylborate and phenylboronic acid. The conditions chosen for this study were dioxane/water (10/1) at 110°C for 18 hours (Table 18). The best yields for each catalyst were obtained with phenylboronic acid under these conditions (Table 18, entries 1, 3 & 5). However the highest enantioselectivity achieved when using phenylboronic acid was a mere 23% (entry 3). However, whilst the yields with the potassium trifluorophenylborate were lower, a promising 43% ee was obtained in combination with the cationic rhodium species $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ in 64% yield. The combination of a neutral catalyst with potassium trifluorophenylborate salt was unsuccessful with barely detectable enantioselectivity with either catalyst (entries 1 & 3).



Entry ^a	Catalyst	Aryl Source	Yield % ^b	ee % ^c
1 ^d	[Rh(acac)(C ₂ H ₄) ₂]	PhB(OH) ₂	72	<5 (S)
2 ^d	[Rh(acac)(C ₂ H ₄) ₂]	PhBF ₃ K	16	<5 (S)
3	[Rh(COD)Cl] ₂	PhB(OH) ₂	65	23 (S)
4	[Rh(COD)Cl] ₂	PhBF ₃ K	<10	<5 (S)
5	[Rh(COD) ₂][PF ₆]	PhB(OH) ₂	91	12 (S)
6	[Rh(COD) ₂][PF ₆]	PhBF ₃ K	64	43 (S)

a Reaction conditions: dimethyl itaconate (1eq.), aryl source (1.2eq), rhodium cat (3mol%), (S)-BINAP (3mol%) in water with SDS (0.5eq.) and Na₂CO₃ (2eq.) for 16h at 80°C.

b isolated yields after flash chromatography

c determined by HPLC analysis using a chiral column (Chiracel OD-H (98:2 Hexane:2-iPrOH))

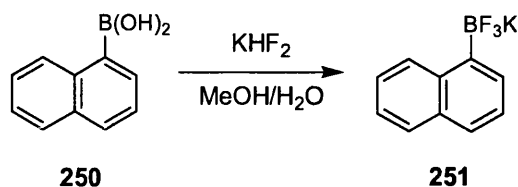
d Reaction conditions: dimethyl itaconate (1eq.), aryl source (5eq.), rhodium cat (3mol%), (S)-BINAP (3.3mol%) in dioxane/H₂O for 18h at 100°C.

Table 18

3.9.2 In Depth Catalyst study

To gain a full insight into the mechanism and the actual active catalyst several parameters were explored. As a better understanding of the catalyst is gained a new catalyst capable of greater enantioselectivity and reactivity may be found. For each of these studies potassium trifluoro(1-naphthyl)borate was used to make dimethyl 1-naphthylsuccinate, a colourless crystalline solid, easily purified by crystallisation giving a well-separated HPLC trace. Potassium trifluoro(1-naphthyl)borate **251** was

obtained a high yield in accordance with a literature procedure from naphthalene boronic acid **250** and potassium difluorohydride (Scheme 95).¹⁰³

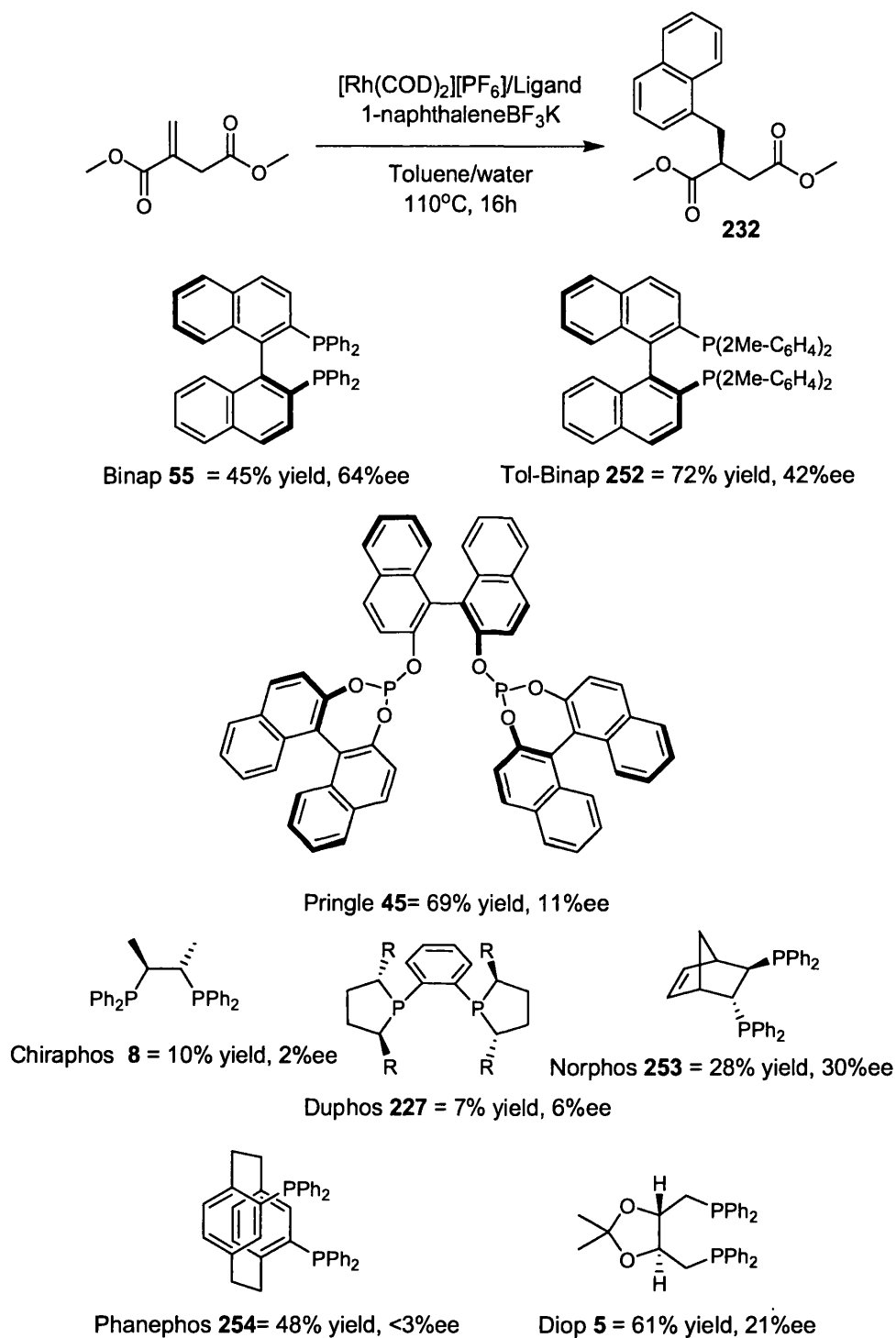


Scheme 95

The first of these small studies examine a variety of bisphosphine ligands and their effect on enantioselectivity.

3.9.3 Ligand study

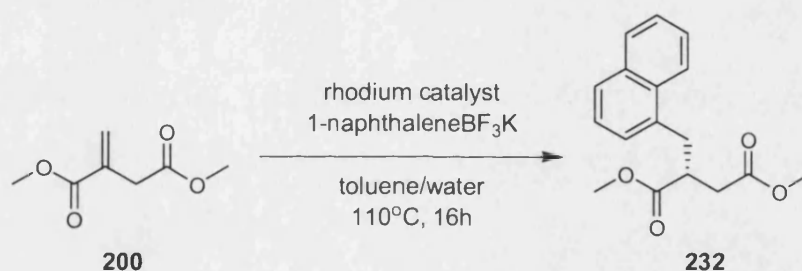
A range of bisphosphine ligands were examined within the reaction all in a 2:1 ratio (ligand:rhodium). As BINAP **55** is well documented as a suitable ligand for rhodium-catalysed 1,4-additions to activated alkenes it was unsurprising that it obtained the highest ee at 64% (Scheme 96). A binaphthyl basis to the ligand seemed to work well with Tol-BINAP **252** making a modest 42% ee although the diphoshite, Pringles ligand, **45** was disappointing with a low 11% ee recorded. Chiraphos **8**, Norphos **253** and Duphos **227** all provided low enantioselectivity with Norphos **253** performing best with 30% ee. Phanephos **254** and DIOP **5** both achieved good yields but again disappointingly low ees (Scheme 96).



Scheme 96

Having established (*R*)-BINAP **246** as the most selective ligand the cationic rhodium catalyst [Rh(COD)((*R*)-BINAP)][PF₆] was preformed to establish if this is the active

catalyst (Table 17). Treatment of dimethylitaconate with potassium trifluoro(1-naphthyl)borate in the presence of 3mol% of preformed catalyst $[\text{Rh}(\text{COD})((R)\text{-BINAP})][\text{PF}_6]$ in toluene/water (20:1) at 110°C for 18 hours affords **232** in an outstanding 72% yield but surprisingly with no enantioselectivity. Interestingly, the addition of one equivalent (to Rh.) of free chiral ligand (*R*)-BINAP to the reaction afforded the addition product with good enantioselectivity (78%ee), but with disappointing reactivity leading to only a 25% yield. It is feasible that the excess ligand could block the free coordination sites on the rhodium, thus, affecting the enantioselective protonation. It was considered that forming the catalyst in situ from $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ and BINAP provided the best compromise between enantioselectivity and yield. Thus it was this catalyst system which was chosen for further optimisation studies.



Entry ^a	Catalyst	Ligand	Yield % ^b	ee % ^c
1	$[\text{Rh}(\text{COD})_2][\text{PF}_6]$	2	45	64 (<i>R</i>)
2	$[\text{Rh}(\text{COD})((R)\text{-BINAP})][\text{PF}_6]$	0	72	0
3	$[\text{Rh}(\text{COD})((R)\text{-BINAP})][\text{PF}_6]$	1	25	78 (<i>R</i>)

a Reaction Conditions : dimethyl itaconate (0.25mmol), potassium trifluoro(1-naphthyl)borate (0.05mmol), Rhodium catalyst(3mol%), toluene (2ml), water (0.25mmol), 110°C , 18 hours.

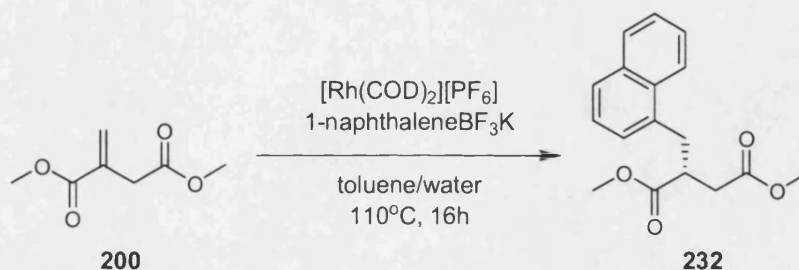
b isolated yields after flash chromatography

c determined by HPLC analysis using chiral column (Chiral OD-H (98:2) Hexane:2-PrOH).

Table 19

3.9.4 Temperature Study

Often an elevated temperature is required in transition metal catalysis to form the active species in the reaction, or to enable the catalyst to turnover. This appears to be the case here as no reaction is observed at room temperature. However at 60°C the catalyst yielded 42% of the addition product, interestingly, with no enantioselectivity (Table 20). This is analogous to the product formed when preformed catalyst $[\text{Rh}(\text{COD})((R)\text{-BINAP})][\text{PF}_6]$ was used without the addition of a second equivalent of (*R*)-BINAP. Whilst the yield here is lower but this can be attributed to the lower temperature affecting the reactivity of the catalyst.



Entry ^a	Temperature °C	Yield % ^b	ee % ^c
1	110	45	64 (<i>R</i>)
2	60	42	0
3	rt	0	0

a Reaction Conditions : dimethyl itaconate (0.25mmol), potassium trifluoro(1-naphthyl)borate (0.05mmol), $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ (3mol%), (*R*)-BINAP (6mol%), toluene (2ml), water (0.25mmol), 18 hours.

b isolated yields after flash chromatography

c determined by HPLC analysis using chiral column (Chiral OD-H (98:2) Hexane:2-PrOH)

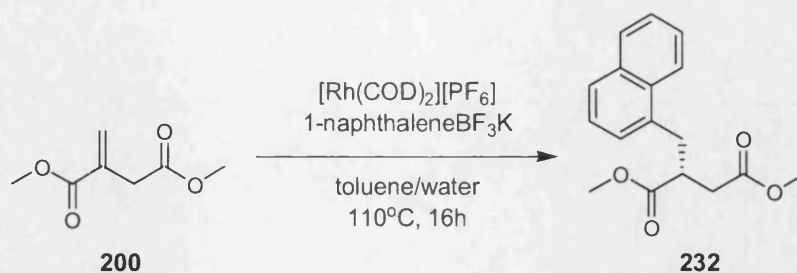
Table 20

3.9.5 Solvent Study

To investigate whether the enantioselectivity and yield could be further increased, a solvent study was carried out. Using the preferred reaction conditions, treatment of dimethylitaconate with potassium trifluoro(1-naphthyl)borate in the presence of 3mol% $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ and (*R*)-BINAP in a solvent/water (20/1) solution at 110°C for 18 hours gave the 2-substituted succinic ester **232** in a range of yields.

The enantioselectivity and yields obtained proved to be highly dependent on the solvent used (Table 21). Generally, very low enantioselectivity was obtained in polar solvents. For example, when the reaction was performed in acetonitrile a racemic product was obtained in moderate yield. The highest yield (87%) was obtained using dioxane, however whilst the yield was high, only a moderate enantioselectivity (42%ee) was obtained. The use of benzonitrile, dichloroethane and hexane also gave moderate enantioselectivity and yields.

The highest enantioselectivities were achieved in aprotic, non-chelating solvents such as toluene and benzene. Interestingly, the highest ee was achieved when the reaction was performed in benzene, whereby the substituted succinic ester **232** was obtained in 56% yield and 82% ee. This is in contrast to the majority of other rhodium catalysed asymmetric 1,4-addition reactions which favour toluene and dioxane.



Entry ^a	Solvent	Yield % ^b	ee % ^c
1	toluene	45	64 (<i>R</i>)
2	dioxane	87	48 (<i>R</i>)
3	benzotrifluoride	53	58 (<i>R</i>)
4	dichloroethane	42	60 (<i>R</i>)
5	acetonitrile	42	0
6	hexane	66	54 (<i>R</i>)
7	benzene	56	82 (<i>R</i>)

a Reaction Conditions : dimethyl itaconate (0.25mmol), potassium trifluoro(1-naphthyl)borate (0.05mmol), $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ (3mol%), solvent (2ml), water (0.25mmol), 18 hours.

b isolated yields after flash chromatography

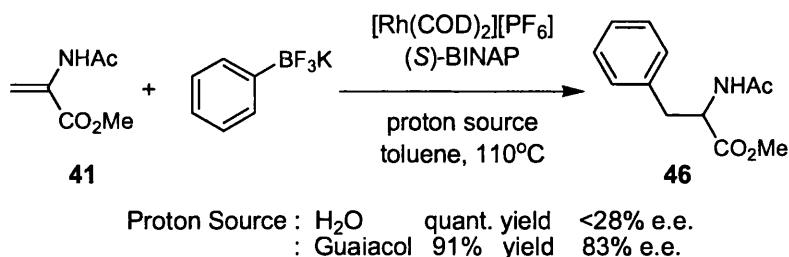
c determined by HPLC analysis using chiral OD-H (98:2) Hexane:2-PrOH

Table 21

3.9.6 Proton Source Study

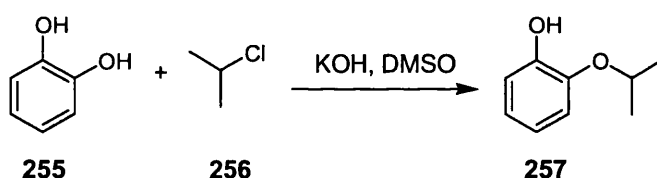
During our research Genet²⁷ reported the asymmetric synthesis of alanine derivatives utilising rhodium-catalysed 1,4-addition. Potassium trifluorophenylborate was added to methyl-2-acetyl-amidoacrylate **41** in the presence of $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ and (*S*)-BINAP in toluene/water (10/1) to yield **46** in quantitative yield but only 28% ee (Scheme 97). Genet and co-workers subsequently investigated a range of proton

sources based on phenol were then tested in anhydrous conditions. The range of enantioselectivities found demonstrated the significance of the proton source in reactions, whereby the enantioselectivity is determined in the protonation step. Guaiacol proved to be the best proton source with an 83% ee being accomplished (Scheme 97).



Scheme 97

Following this, addition of potassium trifluoro(1-naphthyl)borate to dimethyl itaconate in the presence of cationic rhodium complex prepared in situ from $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ and (R)-BINAP in toluene at 110°C using a range of protonating agents based on phenol were examined (Table 22).

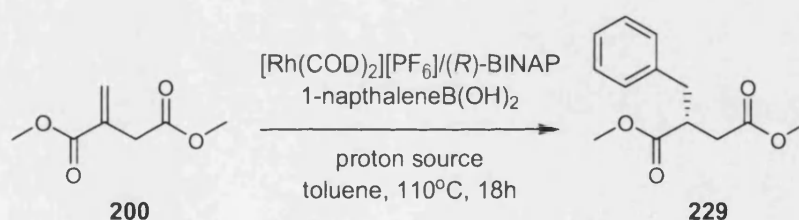


Scheme 98

All proton sources used are commercially available, with the exception of 2-isopropoxyphenol **257**, which was prepared in accordance to literature procedure.¹⁰² Addition of 2-chloropropane to a stirred solution of catechol and potassium hydroxide in DMSO afforded the desired phenol in 20% yield (Scheme 98).

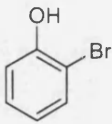
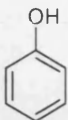
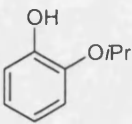
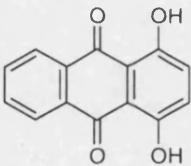
When phenol (**261**) was used as the protonating agent, the addition product was obtained in an excellent yield (100%) but with disappointing enantioselectivity (12%ee). We envisaged the use of phenols with greater steric bulk might force the

protonation to occur from one face preferentially, thus, the use of more sterically hindered proton sources was investigated. Quantitative yields and more significant enantioselectivities were achieved with a range of *ortho*-substituted phenols. It appeared that the enantioselectivity is highly dependant upon the protonating phenol and by increasing steric bulk in the *ortho*-position a decrease in the enantioselectivity is realised. This is contrary to Genet's observations for the addition to methyl 2-acetylamidoacrylate **49**. It appeared that the highest enantioselectivities were obtained using proton sources with the ability to chelate to the rhodium. The use of non-complexing 1-bromophenol **260**, gave an almost racemic product, but in excellent yield whereas 2-isopropoxyphenol **257** and 2-methoxyphenol **258** gave much higher selectivity but in moderate yield. Although it is difficult to rationalise the relation between the level of enantioselectivity and the electronic nature of the *ortho* substituents, the highest ee value was obtained using 2-methoxyphenol (guaiacol) **258** which gave the desired product in 56% yield with 60%ee. However this is still only comparable to the use of water as the protonating agent which also gave the addition product with 60% ee also, but slightly lower yield of 45%.



Entry ^a	Proton Source	Yield % ^b	ee % ^c
1	 258	56	60 (<i>R</i>)
2	 259	60	14 (<i>R</i>)

Table 22 (continued overleaf)

Entry ^a	Proton Source	Yield % ^b	ee % ^c
3	 260	71	2 (<i>R</i>)
4	 261	100	12 (<i>R</i>)
5 ^d	 257	35	38 (<i>R</i>)
6	 262	70	22 (<i>R</i>)
7	H ₂ O	45	60 (<i>R</i>)

a Reaction Conditions : dimethyl itaconate (0.25mmol), potassium trifluoro(1-naphthyl)borate (0.05mmol), [Rh(COD)₂][PF₆] (3mol%), (R)-BINAP (6mol%), toluene (2ml), proton source (0.25mmol), 110°C, 18h.

b isolated yields after flash chromatography

c determined by HPLC analysis using chiral column (Chiral OD-H (98:2) Hexane:2-PrOH)

d in benzene (2ml)

Table 22

3.10 CONCLUSION

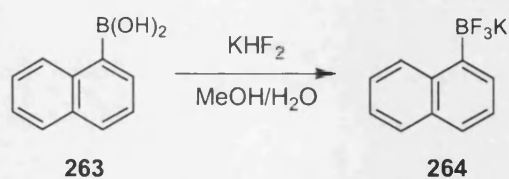
Whilst many of the results recorded in trying to identify a more efficient and enantioselective system, have gone on to confuse the situation we have drawn some worthwhile conclusions from our efforts:

- The application of cationic rhodium catalysts in conjunction with potassium trifluoroorganoborate salts affords both higher chemical yields and enantioselectivities.
- Preforming the rhodium-ligand catalyst by adding a further equivalent of ligand (to rhodium) to the reaction mixture provides higher enantioselectivities, but reduced chemical yields when compared to forming the catalyst *in situ*.
- BINAP is the current ligand of choice for this reaction
- An elevated temperature is essential for the reaction to proceed enantioselectively
- Aromatic alcohols can be used as proton sources, however the best do not provide an enhancement in enantioselectivity over that achieved with water.
- The use of aromatic solvents as the core solvent provides the greatest selectivity.

Thus the optimal conditions for these reactions is to heat the benzene solution of the BF_3K salt (2 equiv.), itaconate ester (1 equiv.) and water (1equiv.) at 110°C in the presence of $[\text{Rh}(\text{COD})_2][\text{PF}_6]/\text{BINAP}$ (1:2). With these conditions in hand we set about the synthesis of a variety of 2-substituted succinic esters through the addition of potassium organotrifluoroborate salts to dimethyl itaconate.

3.11 EXTENDING THE SCOPE

Whilst there are a number of commercially available organoboronic acids exhibiting a variety of functional groups, in comparison very few organo potassium trifluoroborate salts are available. However, the conversion of aryl boronic acids to their potassium trifluoroborate equivalents is a simple high yielding process.

3.11.1 Preparation of BF_3K Salts

Entry ^a	Product	Yield %	Entry ^a	Product	Yield %
1		94	6		83
2		82	7		96
3		81	8		89
4		90	9		86
5		56	10		82

^a Reaction Conditions: Organoboronic acid (1.2 mmol), methanol (3 mL), KHF_2 (4 mmol), rt, 10 minutes.

Table 23

As described previously by Vedejs, treatment of commercially available arylboronic acids with aqueous KHF_2 resulted in precipitation of the potassium

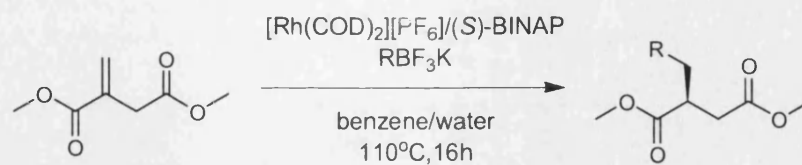
aryltrifluoroborate.^{103,105} After the addition of KHF_2 the solvents were removed in vacuo and the remaining solid was extracted with acetone. Other salts (KBF_4 , KF etc.) are insoluble in acetone hence on removal of the solvent from extracts pure salt was obtained. **Caution: HF is a possible side product from this reaction and so the appropriate care should be taken when handling the reaction medium.**

Through this method an array of BF_3K salts were prepared in high yields (Table 23). It was interesting to note that even though the KHF_2 was strong enough to etch any glassware used there was only a slight drop in yield of product in the presence of some functional groups (Table 23, entries 2, 3, 5 & 6).

3.11.2 1,4-addition of Potassium Trifluoro(organo)borates

The study of the range of potassium trifluoro(organo)borates in the rhodium catalysed 1,4-addition was undertaken in collaboration with Rebecca Moss. In all but one case the 2-substituted succinic esters were produced in excellent yields with significant and consistent enantioselectivity. Both electron-rich and electron-deficient potassium trifluoro(organo)borates were successfully coupled (Table 24). The absolute configuration of the 1,4-addition products were assigned by comparison of the retention time of the previously assigned enantiomers using chiral HPLC. Using (*R*)- or (*S*)- BINAP allowed the formation of (*R*)- or (*S*)- 1,4-addition products with (*R*)-BINAP giving (*R*) configuration of the product. This is consistent with α -*re* face protonation of the oxa- π -allyl rhodium intermediate (Chapter 1).

Potassium trifluorophenylborate achieved the highest enantioselectivity affording 51% yield of 2-benzylsuccinic dimethyl ester in 68% ee. It should be noted that only trace amounts of the *ortho*-methoxy phenyl product was observed, this is attributed to steric hinderance. In contrast to this *para*-methoxy phenyl achieved a high yield of 89-93% and moderate selectivity of 62% ee. Through comparison of *para*-methoxy with *para*-acetyl it can be seen that an electron-donating group in the 4-position enhances the enantioselectivity whereby an electron-withdrawing group detracts. It is pleasing to note that there is very little difference in selectivity between *meta* and *para* substituted substrates.



Entry	Ar-BF ₃ K	Ligand	Product	Yield % ^a	ee % ^b
1		(<i>R</i>)-BINAP	229	51	68 (<i>R</i>)
2		(<i>R</i>)-BINAP	236	Trace	n.d.
3		(<i>R</i>)-BINAP	234	89	62 (<i>R</i>)
		(<i>S</i>)-BINAP	234	93	56 (<i>S</i>)
4		(<i>R</i>)-BINAP	237	75	48 (<i>R</i>)
		(<i>S</i>)-BINAP	237	96	46 (<i>S</i>)
5		(<i>R</i>)-BINAP	275	80	60 (<i>R</i>)
		(<i>S</i>)-BINAP	275	93	54 (<i>S</i>)
6		(<i>R</i>)-BINAP	278	85	58 (<i>R</i>)
		(<i>S</i>)-BINAP	278	95	62 (<i>S</i>)
7		(<i>R</i>)-BINAP	238	89	60 (<i>R</i>)
		(<i>S</i>)-BINAP	238	96	60 (<i>S</i>)

^a Reaction Conditions: dimethyl itaconate (0.25mmol), potassium trifluoro(organoborate) (0.05mmol), [Rh(COD)₂][PF₆] (3mol%), BINAP (6.6mol%), benzene (2ml), water (0.25mmol), 18 hours.

^b isolated yields after flash chromatography

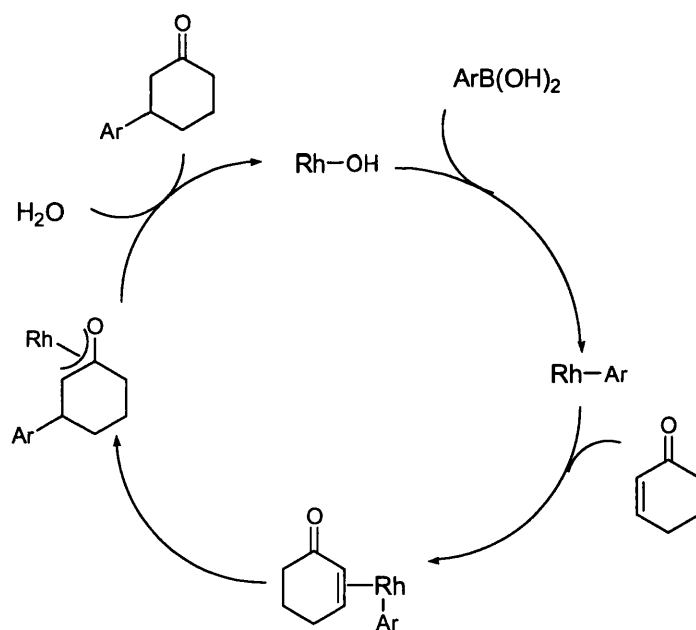
^c determined by HPLC analysis using chiral column (Chiral OD-H (98:2) Hexane:2-PrOH)

Table 24

3.12 CONCLUSION

Despite the wide range of asymmetric 1,4-addition reactions accomplished the asymmetric 1,4-addition to dimethylitaconate is by no means trivial. This is attributed to the fact that when dealing with 1,1-disubstituted substrates the enantioselectivity is determined in the hydrolysis step of the oxa- π -allylrhodium intermediate and not during the insertion step as is the case with most 1,4-addition reactions.⁹⁹

The mechanism for 1,4-addition is explained in detail in section 1.3 of the literature review. Briefly it consists of the formation of the active $[\text{Rh}(\text{OH})]$ catalyst followed by transmetalation of the aryl group between boron and rhodium. Coordination of the alkene is followed by insertion and finally protonolysis to form the product and regenerate the active catalyst (Scheme 99).

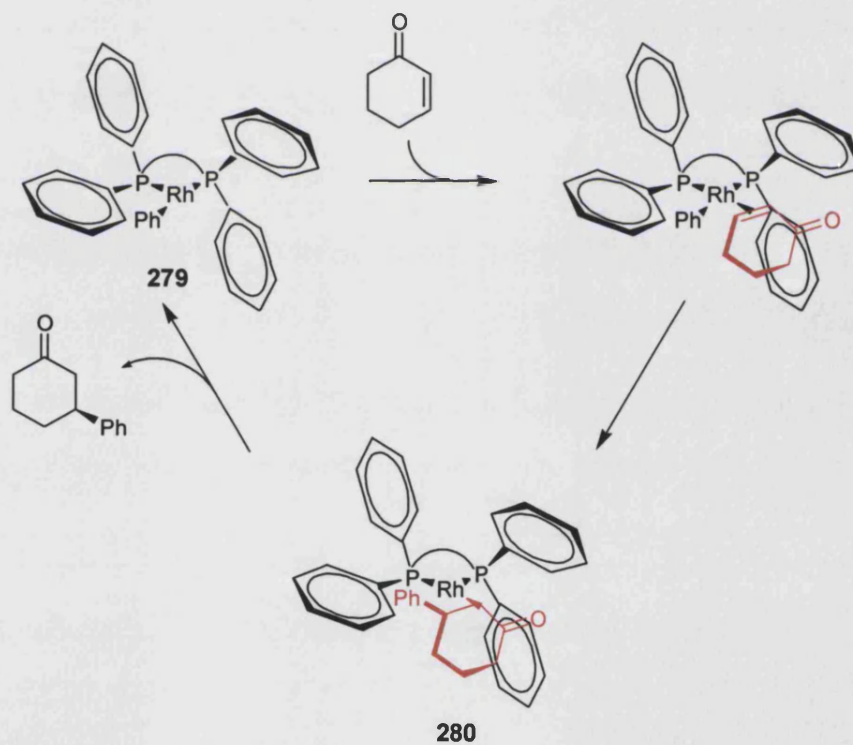


Scheme 99

For additions to 1,2-disubstituted alkenes the chiral centre is formed at the insertion step, thus the coordination of the alkene to the rhodium directly affects the configuration of newly formed chiral centre. The stereochemical pathway of the

mechanism demonstrates how the ligand determines which face the alkene coordinates (Scheme 100).

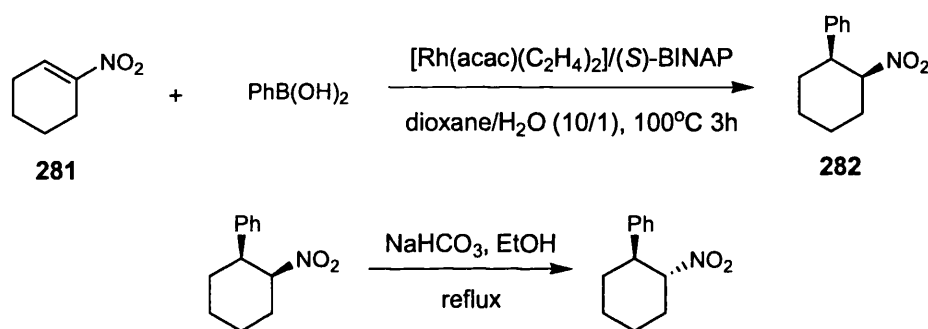
BINAP has been extensively studied and so the skewed structure of **279** is known to reflect its interaction with transition metals. It can be seen that (*S*)-BINAP rhodium intermediate **279** has a free space in the lower part of the coordination site. The upper part being blocked by one of the phenyl rings of the BINAP ligand. This forces the alkene of cyclohexenone to coordinate through its α -si face rather than its α -re face. Migratory insertion then creates a stereocentre in **280** with absolute configuration (*S*). This model can be used to predict a host of 1,4-addition products configuration with the (*S*)-BINAP rhodium intermediate always attacking the α -si face of the α,β -unsaturated carbonyl.



Scheme 100

The situation is complicated further when the protonolysis occurs to form a new chiral centre. For example Hayashi reported that organoboronic acids react with α -

substituted nitroalkenes to form the *cis* isomer in high enantioselectivity. As shown in Scheme 101 phenylboronic acid (5 equiv.) reacts with 1-nitrocyclohexene **281** in the presence of $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]/(S)\text{-BINAP}$ catalyst at 100°C for 3 hours in dioxane/water (10/1) to give **282** in an 89% yield.⁹⁹ Both the *cis* and *trans* diastereoisomers were pure with 98%ee but they appeared in an 87/13 *cis/trans* ratio. It is interesting to note that not only is the *cis* isomer the main product but that this can be converted to the thermodynamically more stable *trans* product simply by refluxing with sodium carbonate with no loss in enantioselectivity. A range of boronic acids reacted well with 1-nitrocyclohexene to produce high yields of 85% *cis* product with between 90-97%ee for both *cis* and *trans* isomers. Unfortunately this reaction does require five equivalents of arylboronic acid due to the elevated temperature so is less economically than would be desired.

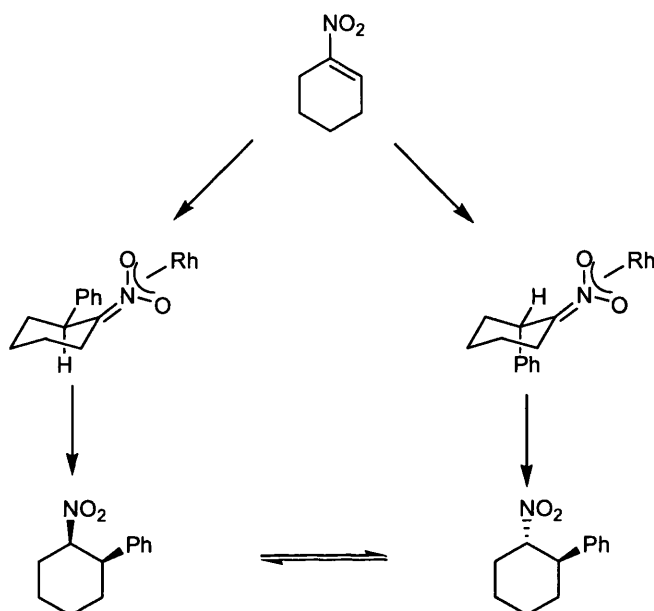


Scheme 101

The origin of the enantioselectivity and the formation of the *cis* product here can be explained by looking at both the mechanism and the stereochemical pathway (Scheme 102).

As with α,β -unsaturated carbonyls transmetallation is followed by coordination of the alkene, then insertion. The same stereochemical model can be used to show that the aryl group will be in the (*S*) configuration if (*S*)-BINAP is used, as the nitro group will occupy the vacant lower quadrant of the catalyst. However, another stereocentre is formed during the protonolysis step. Equatorial protonation results in the formation of the *cis* product and axial protonation the *trans*. Equatorial protonation is favoured due to approach from the less hindered face, thus formation of the *cis* product predominates. The thermodynamically more stable *trans* product

can be formed by reflux in ethanol in the presence of sodium carbonate. As both the *cis* and the *trans* products are formed in 98% enantiomeric purity, it can be seen that the first stereocentre to be generated is fixed.



Scheme 102

Dimethyl itaconate and other 1,1-disubstituted substrates are even more complicated. This is due to the chiral centre not being directly formed directly at the insertion step. Furthermore due to the similar bulk of both substituents on the alkene it is free to coordinate from either the α -si or the α -re face (Scheme 103). The protonation step then forms the chiral centre. This could either happen *via* internal protonation from the already coordinated proton source in a *syn* fashion; or the proton source does not coordinate and protonation occurs from the opposite face to rhodium forming the *anti* product.

Formation of product C could occur *via*:

- Coordination through the α -re face leading to formation of A. Followed by internal *syn* protonation.
- Coordination through the α -si face leading to formation of B. Followed by external *anti* protonation.

Formation of product D could occur *via*:

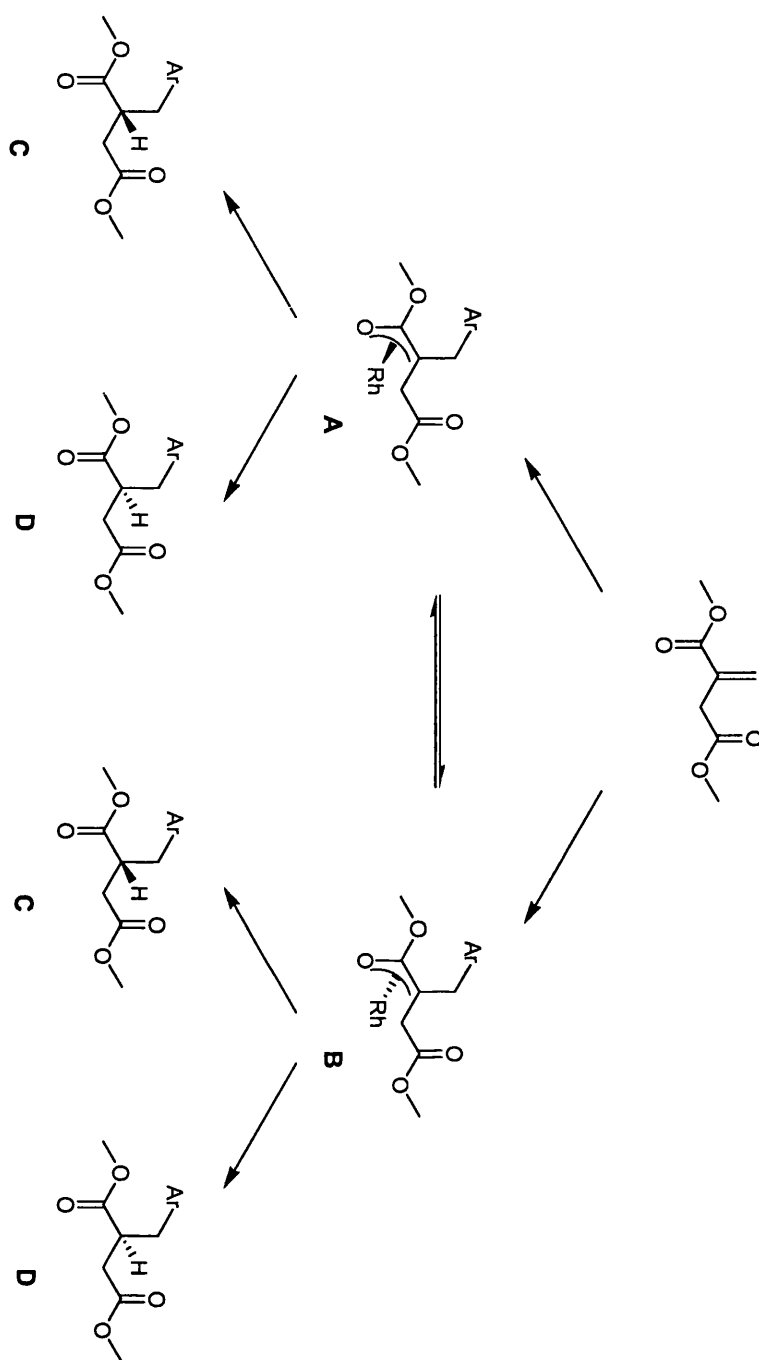
- Coordination through the α -si face leading to formation of B. Followed by internal *syn* protonation.
- Coordination through the α -re face leading to formation of A. Followed by external *anti* protonation.

To further complicate matters it is not known whether the two possible oxa- π -allyl intermediates A and B can interconvert with each other.

If intermediates A and B can interconvert then only racemic product would be produced. As moderate enantioselectivity was achieved this is not the case. However, when $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ with one equivalent of BINAP or $[\text{Rh}(\text{COD})(\text{BINAP})][\text{PF}_6]$ with no added BINAP is used racemic products are formed. This could indicate that the extra equivalent of BINAP prevents this interconversion or that it is unable to block one method of protonation at low temperature. The formation of a racemic mixture when the reaction proceeds at 80°C also supports the theory.

The success of both water and guaiacol as proton sources over phenol and 2-bromophenol suggest that the mechanism proceeds through internal protonation as both of these will coordinate better with the metal centre.

Although extensive further investigation is required I would predict that the mechanism proceeds through a high-energy complex consisting of two equivalents of BINAP forcing the alkene to coordinate through its α -re face followed by internal protonation to produce (*S*)-configuration of the product.



Scheme 103

CHAPTER FOUR:
Experimental

4 EXPERIMENTAL

General Considerations

Commercially available solvents and reagents were obtained from Sigma-Aldrich Company Ltd, Lancaster Synthesis Ltd, Fisher Scientific Ltd and Strem Chemicals UK and were used without further purification, apart from the following: dichloromethane and acetonitrile were distilled from calcium hydride, whilst toluene, tetrahydrofuran, hexane and diethyl ether were distilled from sodium. Solvents and reagents were deoxygenated where necessary by purging with nitrogen. 'Petrol' refers to the fraction of petroleum ether boiling in the range of 40-60°C.

Analytical thin layer chromatography (TLC) was performed using commercially available aluminium backed plates coated with Merck Kieselgel 60 0.20mm (ALUGRAM® sil G/UV₂₅₄) and visualised under ultra-violet light (at 254nm), or by staining with potassium permanganate, vanillin or ninhydrin solution. Flash column chromatography was carried out using Merck Kieselgel 60 H silica gel (particle size: 0.063-0.100mm)

Melting points were determined using a Büchi 535 melting point apparatus and are uncorrected. Infra red spectra (4000 to 600cm⁻¹) were recorded on a Perkin Elmer (1600) FT spectrometer with internal calibration. Elemental analyses were performed with an Exeter analytical, INC. CE-440 elemental analyser in the Chemistry Department at the University of Bath. Fast Atom Bombardment (FAB) and Electron Impact (EI) mss spectra were obtained using a Fisons VG autospec Finnigan MAT 8340 instrument at the University of Bath.

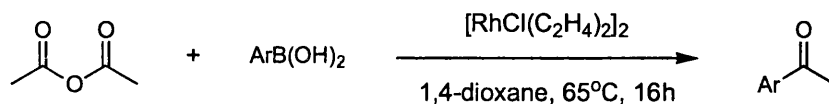
¹H, ¹³C and ¹¹B NMR spectra were recorded on a Joel EX-400, Brücker DPX-300 or a Joel GX-270 spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm), referenced to an internal SiMe₄ standard for ¹H-NMR, and relative to solvent for ¹³C-NMR and ¹¹B-NMR. The multiplicities of the spectroscopic data are presented in the following manner: singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), and multiplet (m). Coupling constants (*J*) are expressed in Hertz (Hz). The assignment of aromatic proton

resonances for *para* disubstituted benzene rings has been simplified by assuming an AB system, however the characteristic features of an AA'BB' system were observed in the NMR spectra.

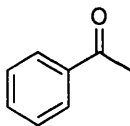
High Performance Liquid Chromatography (HPLC) was performed on TSP Thermo Separation Product Spectra series system, which uses chiral columns such as Chiralpak OD-H by Daicel Chemical Ind. Ltd.

4.1 PREPARATION OF KETONES VIA THE RHODIUM-CATALYSED ADDITION OF ARYLBORONIC ACIDS TO ANHYDRIDES

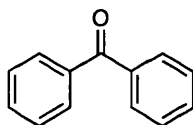
General Procedure



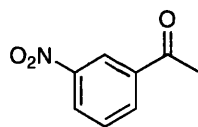
To a pressure-tube charged with [RhCl(C₂H₄)₂]₂ (0.01g, 0.024 mmol, 1.5 mol%) was added 1,4-dioxane (6 mL), boronic acid (2.24 mmol, 1.4 equiv.) and anhydride (1.6 mmol). The tube was sealed, placed in a cold oil bath which, then heated to 65°C and stirred for 16 hours. The mixture was allowed to cool to room temperature and diluted with water (10 mL) and the product extracted into ethyl acetate (3 × 10 mL), the combined extracts were washed with brine (3 x 10 mL), dried over magnesium sulphate and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (ethyl acetate:hexane, 1:8 by volume) to afford the desired aryl ketone.

Acetophenone (170)

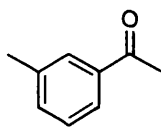
Acetic anhydride (0.163 g, 1.6 mmol) and phenylboronic acid (0.273 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a colourless oil (0.167 g, 87% yield); R_f (petrol:ethyl acetate 8:1) 0.36; ν_{\max} (KBr/Nujol)/ cm^{-1} 1730 (C=O); δ_H (300 MHz; CDCl_3) 7.8 -7.9 (2H, m, Ar), 7.3 -7.5 (3H, m, Ar), 2.50 (3H, s, CH_3); δ_C (75.5 MHz; CDCl_3) 198.3, 137.4, 133.4, 128.9, 128.6, 26.9. Data identical to those in literature¹⁰⁶.

Benzophenone (180)

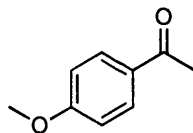
Benzoic anhydride (0.362 g, 1.6 mmol) and phenylboronic acid (0.273 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a colourless crystalline solid (0.22 g, 76% yield) mp (hexane) 50-51°C; R_f (Petrol: ethyl acetate 12:1) 0.39; ν_{\max} (Nujol)/ cm^{-1} 1655 (C=O); δ_H (300 MHz; CDCl_3) 7.9 - 7.8 (4H, m, Ar), 7.6 - 7.5 (2H, m, Ar), 7.5 - 7.3 (2H, m, Ar); δ_C (75.5 MHz; CDCl_3) 197.1, 138.0, 132.8, 130.5, 128.7. Data identical to those in literature.¹¹⁵

1-(3-Nitrophenyl)ethanone (181)

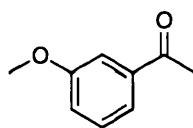
Acetic anhydride (0.163 g, 1.6 mmol) and 3-nitrophenylboronic acid (0.374 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a pale yellow solid (0.148 g, 56% yield), mp 75-77°C; R_f (petrol:ethyl acetate 8:1) 0.47; ν_{\max} (Nujol)/cm⁻¹ 1690 (C=O); δ_H (300 MHz; CDCl₃) 8.8-8.9 (1H, m, Ar), 8.3 - 8.5 (3H, m, Ar); δ_C (75.5 MHz; CDCl₃) 195.6, 148.4, 138.2, 133.7, 129.8, 127.3, 123.1, 26.6. Data identical to those in literature.¹⁰⁷

1-*m*-Tolylethanone (182)

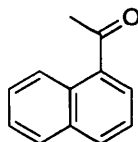
Acetic anhydride (0.163 g, 1.6 mmol) and 3-methylphenylboronic acid (0.305 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.146 g, 68% yield); R_f (petrol:ethyl acetate 8:1) 0.43; ν_{\max} (Nujol)/cm⁻¹ 1675 (C=O); δ_H (300 MHz; CDCl₃) 7.7-7.6 (2H, m, Ar), 7.3-7.1 (2H, m, Ar), 2.46 (3H, s, CH₃), 2.82 (3H, s, CH₃); δ_C (75.5 MHz; CDCl₃) 198.9, 138.7, 137.5, 134.2, 129.2, 128.8, 125.9, 27.0, 21.7. Data identical to those in literature.¹⁰⁸

1-(4-Methoxyphenyl)ethanone (183)

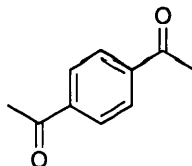
Acetic anhydride (0.163 g, 1.6 mmol) and 4-methoxyphenylboronic acid (0.340 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a colourless solid (0.161 g, 67% yield) mp (hexane) 38-39°C; R_f (Petrol: ethyl acetate 8:1) 0.33; ν_{\max} (Nujol)/cm⁻¹ 2850 (OCH₃), 1665 (C=O); δ_H (300 MHz; CDCl₃) 7.93 (2H, d, J 8.6 Hz, Ar), 6.92 (2H, d, J 8.6 Hz, Ar), 3.86 (3H, s, OCH₃), 2.55 (3H, s, CH₃); δ_C (75.5 MHz; CDCl₃) 197.1, 163.9, 131.0, 130.7, 112.1, 55.8, 26.7. Data identical to those in literature.¹¹³

1-(3-Methoxyphenyl)ethanone (184)

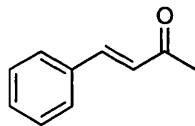
Acetic anhydride (0.163 g, 1.6 mmol) and 3-methoxyphenylboronic acid (0.340 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.17 g, 69% yield); R_f (petrol:ethyl acetate 8:1) 0.32; ν_{\max} (Nujol)/cm⁻¹ 2837 (OCH₃), 1691 (C=O); δ_H (300 MHz; CDCl₃) 7.44 (2H, t, J 8.9 Hz, Ar), 7.28 (1H, t, J 8.9 Hz, Ar), 7.1-7.0 (1H, m, Ar), 3.75 (3H, s, OCH₃), 2.50 (3H, s, CH₃); δ_C (75.5 MHz; CDCl₃) 197.6, 159.6, 138.3, 128.9, 120.9, 119.5, 112.2, 55.4, 26.8. Data identical to those in literature.¹¹³

1-(Naphthalen-4-yl)ethanone (185)

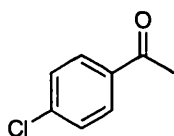
Acetic anhydride (0.163 g, 1.6 mmol) and 1-naphthaleneboronic acid (0.385 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a colourless oil (0.21 g, 76% yield); R_f (petrol:ethyl acetate 8:1) 0.30; ν_{\max} (Nujol)/ cm^{-1} 1680 (C=O); δ_H (300 MHz; CDCl_3) 8.80 (1H, d, J 8.5 Hz, Ar), 8.0 – 7.9 (3H, m, Ar), 7.6 – 7.5 (3H, m, Ar), 2.73 (3H, s, CH_3); δ_C (75.5 MHz; CDCl_3) 202.2, 135.8, 134.4, 133.4, 130.6, 129.2, 128.9, 128.2, 127.1, 126.9, 126.5, 30.9. Data identical to those in literature.¹¹⁴

1,4-Diacetylbenzene (186)

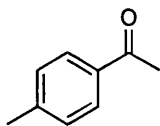
Acetic anhydride (0.163 g, 1.6 mmol) and 4-acetylphenylboronic acid (0.367 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a colourless crystalline solid (0.223 g, 86% yield); mp 112-114°C; R_f (petrol:ethyl acetate 8:1) 0.51; ν_{\max} (Nujol)/ cm^{-1} 1692 (C=O); δ_H (300 MHz; CDCl_3) 8.00 (4H, s, Ar), 2.65 (3H, s, CH_3); δ_C (75.5 MHz; CDCl_3) 197.5, 140.2, 129.3, 27.1. Data identical to those in literature.¹¹²

(E)-4-Phenylbut-3-en-2-one (187)

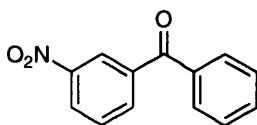
Acetic anhydride (0.163 g, 1.6 mmol) and *trans*-2-phenylvinylboronic acid (0.331 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a colourless solid (0.13 g, 54% yield) mp (petrol) 37-39°C; R_f (petrol:ethyl acetate 8:1) 0.26; ν_{\max} (Nujol)/cm⁻¹ 1682 (C=O), 1605 (C=C); δ_H (300 MHz; CDCl₃) 7.8-7.6 (5H, m, Ar), 7.46 (2H, d J 16.1 Hz, C=C), 6.71 (2H, d J 16.1 Hz, C=C), 2.37 (3H, s, CH₃); δ_C (75.5 MHz; CDCl₃) 198.3, 143.4, 134.4, 130.5, 128.9, 128.2, 127.1, 27.4. Data identical to those in literature.¹¹⁰

1-(4-Chlorophenyl)ethanone (188)

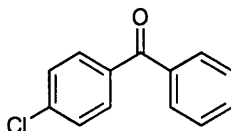
Acetic anhydride (0.163 g, 1.6 mmol) and 4-chlorophenylboronic acid (0.349 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a colourless oil (0.19 g, 78% yield); R_f (petrol:ethyl acetate 8:1) 0.37; ν_{\max} (Nujol)/cm⁻¹ 1685 (C=O); δ_H (300 MHz; CDCl₃) 7.80 (2H, d, J 8.7 Hz, Ar), 7.58 (2H, d, J 8.7 Hz, Ar), 2.56 (3H, s, CH₃); δ_C (75.5 MHz; CDCl₃) 197.4, 136.2, 132.3, 131.9, 130.2, 129.7, 26.9. Data identical to those in literature.¹¹¹

1-*p*-Tolylethanone (189)

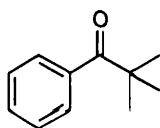
Acetic anhydride (0.163 g, 1.6 mmol) and 4-methylphenylboronic acid (0.305 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a colourless oil (0.13 g, 62% yield); R_f (petrol:ethyl acetate 8:1) 0.42; ν_{\max} (Nujol)/ cm^{-1} 1680 (C=O); δ_H (300 MHz; CDCl_3) 7.86 (2H, d, J 8.4 Hz, Ar), 7.26 (2H, d, J 8.4 Hz, Ar), 2.58 (3H, s, CH_3), 2.41 (3H, s, CH_3); δ_C (75.5 MHz; CDCl_3) 198.9, 143.9, 134.7, 129.3, 128.5, 26.6, 21.7. Data identical to those in literature.¹⁰⁹

(3-Nitrophenyl)(phenyl)methanone (190)

Benzoic anhydride (0.362 g, 1.6 mmol) and 3-nitrophenylboronic acid (0.374 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a yellow crystalline solid (0.21 g, 59% yield) mp (ethyl acetate) 92-5°C; R_f (petrol:ethyl acetate 12:1) 0.15; ν_{\max} (Nujol)/ cm^{-1} 1655(C=O), 1538 (CNO₂), 1280 (CNO₂); δ_H (300 MHz; CDCl_3) 8.0 – 8.2 (4H, m, Ar), 7.6 – 7.5 (5H, m, Ar); δ_C (75.5 MHz; CDCl_3) 199.8, 139.1, 136.2, 135.5, 133.4, 129.9, 129.6, 128.7, 126.7, 124.6. Data identical to those in literature.¹¹⁵

(4-Chlorophenyl)(phenyl)methanone (191)

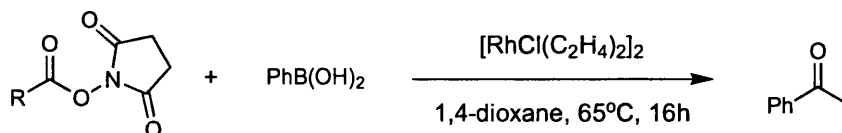
Benzoic anhydride (0.362 g, 1.6 mmol) and 4-chlorophenylboronic acid (0.349 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a pale yellow powder (0.22 g, 63% yield) mp 78°C; R_f (petrol:ethyl acetate 12:1) 0.18; ν_{\max} (Nujol)/ cm^{-1} 1670 (C=O); δ_H (300 MHz; CDCl_3) 8.2 – 8.0 (4H, m, Ar), 7.5 – 7.3 (5H, m, Ar); δ_C (75.5 MHz; CDCl_3) 196.6, 137.5, 136.8, 136.7, 133.1, 132.8, 131.4, 129.4, 127.9. Data identical to those in literature.¹¹⁵

2,2-Dimethyl-1-phenylpropan-1-one (197)

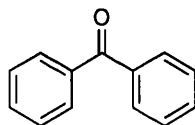
Trimethylacetic anhydride (0.298 g, 1.6 mmol) and phenylboronic acid (0.273 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a yellow oil (0.07 g, 28% yield); R_f (petrol:ethyl acetate 12:1) 0.22; ν_{\max} (Nujol)/ cm^{-1} 1680 (C=O); δ_H (300 MHz; CDCl_3) 7.7 – 7.6 (2H, m, Ar), 7.4 – 7.3 (3H, m, Ar), 1.35 (9H, s, CH_3); δ_C (75.5 MHz; CDCl_3) 209.6, 130.8, 129.8, 128.7, 129.6, 128.4, 128.2, 44.6, 28.62, 28.4, 28.2. Data identical to those in literature.¹¹⁶

4.2 PREPARATION OF KETONES VIA THE RHODIUM-CATALYSED ADDITION OF ARYLBORONIC ACIDS TO *N*-HYDROXYSUCCINIMIDE (NHS) ESTERS

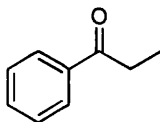
General Procedure



To a Pressure tube charged with [RhCl(C₂H₄)₂]₂ (0.024 mmol, 1.5 mol%) was added 1,4-dioxane (6 mL), boronic acid (2.24 mmol, 1.4 equiv.) and the NHS ester (1.6 mmol). The tube was sealed, placed in a cold oil bath, then heated to 65°C and stirred for 16 hours. The mixture was allowed to cool to room temperature and diluted with water (10 mL) and the product extracted into ethyl acetate (3 × 10 mL), the combined extracts were washed with brine (3 × 10 mL), dried over magnesium sulphate and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (ethyl acetate:petrol, 1:8 by volume) to afford the desired aryl ketone.

Benzophenone (180)

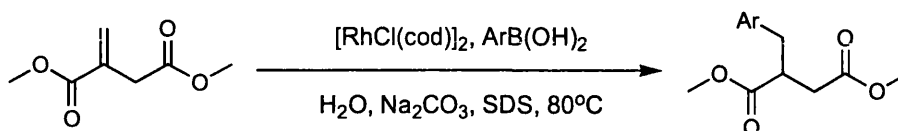
1-Benzoylpyrrolidine-2,5-dione (0.325 g, 1.6 mmol) and phenylboronic acid (0.273 g, 2.24 mmol), were reacted under the standard protocol to generate the desired compound as a colourless crystalline solid (0.18 g, 64% yield) mp (hexane) 50-51°C; R_f (petrol:ethyl acetate 12:1) 0.39; ν_{\max} (Nujol)/cm⁻¹ 1655 (C=O) ; δ_H (300 MHz; CDCl₃) 7.79 (4H, m, Ar), 7.57 (2H, m, Ar), 7.46 (2H, m, Ar); δ_C (75.5 MHz; CDCl₃) 197.1, 138.0, 132.8, 130.5, 128.7. Data identical to those in literature.¹¹⁵

Propiophenone (198)

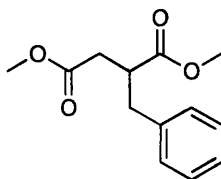
1-Propionylpyrrolidine-2,5-dione (0.248 g, 1.6 mmol) and phenylboronic acid (0.273 g, 2.24 mmol), were reacted under the standard protocol to generate the desired ketone as a colourless oil (0.09 g, 43% yield); R_f (petrol:ethyl acetate 4:1) 0.48; ν_{\max} (Nujol)/cm⁻¹ 1655 (C=O); δ_H (300 MHz; CDCl₃) 7.94 (2H, d, J 7.2 Hz, Ar), 7.5 – 7.4 (3H, m, Ar), 2.96 (2H, q, J 7.2 Hz, CH₂), 1.20 (3H, t, J 7.2 Hz, CH₃); δ_C (75.5 MHz; CDCl₃) 201.1, 137.3, 133.2, 129.2, 128.9, 128.7, 128.5, 32.1. Data identical to those in literature.¹¹¹

4.3 RHODIUM-CATALYSED ADDITION OF ARYLBORONIC ACIDS TO ITACONATE ESTERS IN WATER.

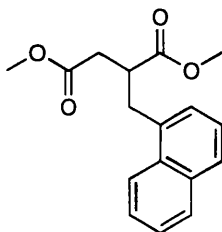
General Procedure



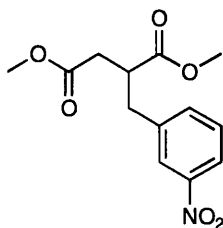
To a solution of $[\text{RhCl(COD)}]_2$ (0.012 g, 0.058 mmol, 2 mol%) in water (6.6 mL) was added dimethyl itaconate (0.21 g, 1.308 mmol), boronic acid (3.36 mmol, 2.5 equiv.), sodium dodecyl sulphate (0.189 g, 0.684 mmol, 0.5 equiv.) and sodium carbonate (0.291 g, 3.648 mmol, 2 equiv.). The resulting solution was stirred at 80°C for 16 hours. The mixture was allowed to cool to room temperature the product extracted with diethyl ether (3×15 mL), the combined extracts were washed with brine (3×15 mL), dried over magnesium sulphate and concentrated *in vacuo*. The crude product was then purified by flash chromatography (ethyl acetate:petrol, 1:4 by volume).

Dimethyl 2-benzylsuccinate (229)

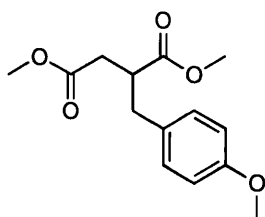
Dimethyl itaconate (0.21 g, 1.308 mmol) and phenylboronic acid (0.410 g, 3.36 mmol), were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.26 g, 85% yield); R_f (petrol:ethyl acetate, 9:1) 0.2; ν_{\max} (Nujol)/ cm^{-1} 1736 (C=O); δ_H (300 MHz; CDCl_3) 7.2 – 7.1 (5H, m, Ar), 3.60 (3H, s, CH_3), 3.57 (3H, s, CH_3), 3.2 - 3.1 (2H, m, CH_2 , CH), 2.7 - 2.9 (2H, m, CH_2), 2.34 (1H, dd, J 4.8, 16.8 Hz, CH_2); δ_C (75.5 MHz; CDCl_3) 175.0, 172.6, 138.5, 129.4, 128.9, 127.4, 52.3, 52.1, 43.4, 38.1, 35.2; m/z (FAB+) 237. Data identical to those in literature.¹¹⁹

dimethyl 2-((naphthalen-1-yl)methyl)succinate (232)

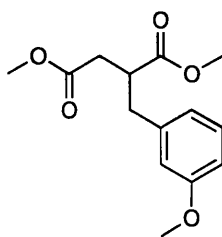
Dimethyl itaconate (0.21 g, 1.308 mmol) and 1-naphthaleneboronic acid (0.578 g, 3.36 mmol), were reacted under the standard protocol to generate the desired compound as colourless crystalline needles (0.30 g, 81% yield); mp (hexane) 96°C; R_f (petrol:ethyl acetate, 9:1) 0.16; ν_{\max} (Nujol)/cm⁻¹ 1719 (C=O), 1050 (C-O); δ_H (300 MHz; CDCl₃) 8.02 (1H, d, J 8.7 Hz, Ar), 7.80 (1H, d, J 9.3 Hz, Ar), 7.69 (1H, d, J 8.4 Hz, Ar), 7.46 (2H, m, Ar), 7.32 (1H, t, J 6.9 Hz, Ar), 7.21 (1H, d, J 8.1 Hz, Ar), 3.61 (3H, s, OCH₃), 3.4 -3.5 (4H, m, CH₂, OCH₃), 3.24 (1H, m, CH), 3.06 (1H, dd, J 9.3, 13.5 Hz, CH₂), 2.69 (1H, dd, J 9.3, 17.1 Hz, CH₂), 2.37 (1H, dd, J 5.1, 17.1 Hz, CH₂); δ_C (75.5 MHz; CDCl₃) 172.6, 175.3, 134.6, 134.4, 132.1, 129.3, 128.1, 127.8, 126.7, 126.1, 125.7, 123.9, 52.4, 52.1, 42.5, 35.6, 35.5; m/z (FAB+) 286 (56%, $M^+ + H$) [found 286.121048 $M^+ + H$ C₁₇H₁₈O₄ requires M 286.120509]; Anal. Calc'd for C₁₇H₁₈O₄; C, 71.31; H, 6.34; N, 0.00. Found: C, 71.3; H, 6.34; N, 0.00. Data identical to those in literature.¹¹⁷

Dimethyl 2-(3-nitrobenzyl)succinate (233)

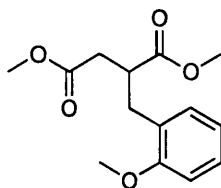
Dimethyl itaconate (0.21 g, 1.308 mmol) and 3-nitrophenylboronic acid (0.561 g, 3.36 mmol), were reacted under the standard protocol to generate the desired compound as a pale brown solid (0.21 g, 56% yield); R_f (petrol:ethyl acetate, 9:1) 0.16; ν_{\max} (Nujol)/ cm^{-1} 1746 (C=O), 1461 (CNO₂), 1376 (CNO₂), 1168 (C-O); δ_{H} (300 MHz; CDCl₃) 8.0 (2H, m, Ar), 7.4 (2H, m, Ar), 3.60 (6H, s, OCH₃), 3.1 (2H, m, CH, CH₂), 2.88 (1H, dd, J 10.5, 16.8 Hz, CH₂), 2.65 (1H, dd, J 8.7, 17.1 Hz, CH₂), 2.39 (1H, dd, J 5.7, 17.1 Hz, CH₂); δ_{C} (75.5 MHz; CDCl₃) 172.1, 171.4, 140.7, 135.6, 129.8, 124.2, 122.3, 52.4, 52.3, 50.8, 37.4, 35.4; m/z (FAB+) 282 ($\text{M}^{\text{+}}\text{H}$).

Dimethyl 2-(4-methoxybenzyl)succinate (234)

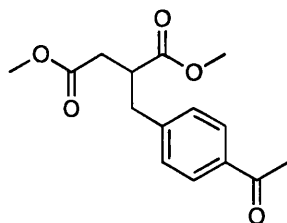
Dimethyl itaconate (0.21 g, 1.308 mmol) and 4-methoxyphenylboronic acid (0.511 g, 3.36 mmol), were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.21 g, 64% yield); R_f (petrol:ethyl acetate, 9:1) 0.14; ν_{\max} (Nujol)/ cm^{-1} 2852 (OCH₃), 1746 (C=O), 1196 (C-O), 1132 (C-O); δ_H (300 MHz; CDCl₃) 7.0 (2H, d, J 8.7 Hz, Ar), 6.76 (2H, d, J 8.7 Hz, Ar), 3.72 (3H, s, ArOCH₃), 3.60 (3H, s, CH₃), 3.57 (3H, s, CH₃), 3.1 - 2.8 (2H, m, CH₂, CH), 2.7 - 2.5 (2H, m, CH₂), 2.33 (1H, dd, J 5.1, 16.8 Hz, CH₂); δ_C (75.5 MHz; CDCl₃) 175.1, 172.7, 158.8, 130.5, 130.4, 116.4, 115.1, 114.8, 55.6, 52.3, 52.1, 43.6, 37.3, 35.3; m/z (FAB+) 267 (41% $M^+ + H$) [267.121910 found $M^+ + H$ C₁₄H₁₉O₅ requires M 267.123249].

Dimethyl 2-(3-methoxybenzyl)succinate (235)

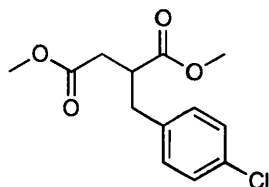
Dimethyl itaconate (0.21 g, 1.308 mmol) and 3-methoxyphenylboronic acid (0.511 g, 3.36 mmol), were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.23 g, 67% yield); R_f (petrol:ethyl acetate, 9:1) 0.09; ν_{\max} (Nujol)/ cm^{-1} 2846 (OCH_3), 1744 ($\text{C}=\text{O}$), 1214 ($\text{C}-\text{O}$), 1142 ($\text{C}-\text{O}$); δ_{H} (300 MHz; CDCl_3) 7.12 (1H, t, J 7.6 Hz, Ar), 6.7 – 6.5 (3H, m, Ar), 3.70 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.56 (3H, s, OCH_3), 3.1 – 2.9 (2H, m, CH, CH_2), 2.7 – 2.5 (2H, m, CH_2), 2.33 (1H, dd, J 4.9, 12.2 Hz, CH_2); δ_{C} (75.5 MHz; CDCl_3) 175.0, 172.7, 160.4, 140.1, 129.9, 121.8, 115.0, 112.5, 65.5, 58.3, 52.4, 48.3, 38.4, 35.2; m/z (FAB+) 267 (80% $\text{M}^+ + \text{H}$) [267.123100 found $\text{M}^+ + \text{H}$ $\text{C}_{14}\text{H}_{19}\text{O}_5$ requires M 267.123249]; Data identical to those in literature.¹¹⁸

Dimethyl 2-(2-methoxybenzyl)succinate (236)

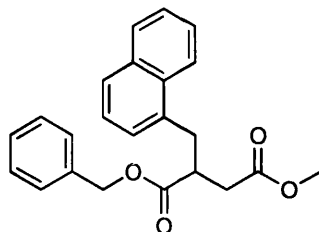
Dimethyl itaconate (0.21 g, 1.308 mmol) and 2-methoxyphenylboronic acid (0.511 g, 3.36 mmol), were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.27 g, 78% yield); R_f (petrol:ethyl acetate, 9:1) 0.09; ν_{\max} (Nujol)/ cm^{-1} 2853 (OCH₃), 1748 (C=O), 1245 (C-O), 1160 (C-O); δ_{H} (300 MHz; CDCl₃) 7.2 – 7.1 (1H, m, Ar), 6.99 (1H, d, J 5.6 Hz, Ar), 6.8 – 6.7 (2H, m, Ar), 3.74 (3H, s, OCH₃), 3.58 (3H, s, OCH₃), 3.55 (3H, s, OCH₃), 3.2 – 3.1 (1H, m, CH), 2.97 (1H, dd, J 6.5, 13.5 Hz, CH₂), 2.69 (1H, dd, J 8.4, 13.2 Hz, CH₂), 2.60 (1H, dd, J 9.7, 17.0 Hz, CH₂), 2.32 (1H, dd, J 4.9, 17.0 Hz, CH₂); δ_{C} (75.5 MHz; CDCl₃) 175.5, 172.8, 158.0, 131.2, 128.5, 126.8, 120.7, 110.7, 55.6, 52.4, 52.0, 41.7, 35.4, 32.9; m/z (FAB+) 267 (41% $\text{M}^{\dagger}+\text{H}$) [267.121910 found $\text{M}^{\dagger}+\text{H}$ C₁₄H₁₉O₅ requires M 267.123249].

Dimethyl 2-(4-acetylbenzyl)succinate (237)

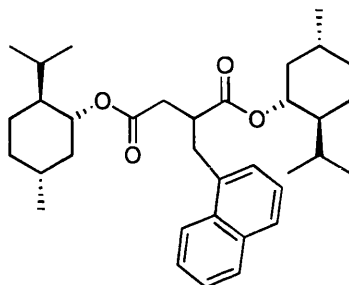
Dimethyl itaconate (0.21 g, 1.308 mmol) and 4-acetylphenylboronic acid (0.551 g, 3.36 mmol), were reacted under the standard protocol to generate the desired succinate as a pale yellow oil (0.27 g, 73% yield); R_f (petrol:ethyl acetate, 9:1) 0.08; ν_{\max} (Nujol)/ cm^{-1} 1750 (C=O), 1684 (C=O), 1267 (C-O), 1167 (C-O); δ_{H} (300 MHz; CDCl_3) 7.82 (2H, d, J 8.4 Hz, Ar), 7.19 (2H, d, J 8.4 Hz, Ar), 3.59 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.1 – 2.9 (2H, m, CH, CH_2), 2.78 (1H, dd, J 7.2, 13.1 Hz, CH_2), 2.62 (1H, dd, J 8.1, 16.4 Hz, CH_2), 2.51 (3H, s, CH_3), 2.34 (1H, dd, J 5.2, 16.4 Hz,); δ_{C} (75.5 MHz; CDCl_3) 198.1, 174.6, 172.4, 144.2, 135.4, 129.6, 129.4, 129.0, 127.8, 53.8, 52.4, 43.1, 37.9, 35.4, 26.9; m/z (FAB+) 279 (95%, $\text{M}^+ + \text{H}$) [found 279.124176 $\text{M}^+ + \text{H}$ $\text{C}_{15}\text{H}_{19}\text{O}_5$ requires M 279.123249].

Dimethyl 2-(4-chlorobenzyl)succinate (238)

Dimethyl itaconate (0.21 g, 1.308 mmol) and 4-chlorophenylboronic acid (0.524 g, 3.36 mmol), were reacted under the standard protocol to generate the desired compound as a pale yellow crystalline needles (0.24 g, 69% yield); mp (ethanol) 42-44°C; R_f (petrol:ethyl acetate, 9:1) 0.19; ν_{\max} (Nujol)/cm⁻¹ 1744 (C=O), 1161 (C-O), 1094 (C-O); δ_H (300 MHz; CDCl₃) 7.18 (2H, d, J = 8.4, Ar), 7.01 (2H, d, J 8.4 Hz, Ar), 3.59 (3H, s, CH₃), 3.57 (3H, s, CH₃), 3.0 (2H, m, CH, CH₂), 2.6 (2H, m, CH₂), 2.33 (1H, dd, J 5.7, 17.1 Hz, CH₂); δ_C (75.5 MHz; CDCl₃) 174.7, 172.4, 137.03, 132.9, 130.7, 129.1, 52.3, 52.2, 43.3, 37.4, 35.3; m/z (FAB+) 271 (80% $M^+ + H$) [271.07353 found $M^+ + H$ C₁₃H₁₆O₄³⁵Cl₁ requires M 271.073712].

1-Benzyl 4-methyl 2-((naphthalen-1-yl)methyl)succinate (247)

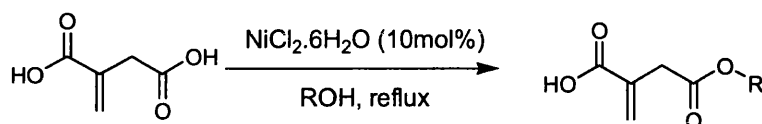
4-Benzyl 1-methyl 2-methylenesuccinate (0.016 g, 0.07 mmol) and 1-naphthylboronic acid (0.031 g, 0.18 mmol), were reacted under the standard protocol to generate the desired compound as a yellow oil (0.007 g, 28% yield); R_f (petrol:ethyl acetate, 4:1) 0.12; δ_H (300 MHz; $CDCl_3$) 7.92 (1H, d, J 8.6 Hz, Ar), 7.71 (1H, d, J 8.9 Hz, Ar), 7.68 (1H, d, J 8.4 Hz, Ar), 7.5 – 7.4 (2H, m, Ar), 7.3 – 7.1 (2H, m, Ar), 5.02 (2H, s, CH_2), 3.47 (3H, s, CH_3), 3.5 – 3.4 (1H, m, CH_2), 3.4 – 3.2 (1H, m, CH), 3.18 (1H, dd, J 9.4, 15.6 Hz, CH_2), 2.67 (1H, dd, J 8.9, 17.1 Hz, CH_2), 2.34 (1H, dd, J 9.2, 17.5 Hz, CH_2). Due to only a small amount of material available no further data was able to be collected.

Bis((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2-((naphthalen-8-yl)methyl)succinate (248)

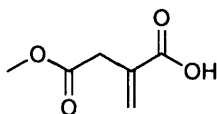
Bis((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2-methylenesuccinate (0.03 g, 0.07 mmol) and 1-naphthylboronic acid (0.031 g, 0.18 mmol), were reacted under the standard protocol to generate the desired compound as a yellow oil (0.018 g, 49% yield); R_f (petrol:ethyl acetate, 4:1) 0.2; δ_H (300 MHz; $CDCl_3$) 8.1 – 7.9 (1H, m, Ar), 7.8 – 7.7 (3H, m, Ar), 7.5 – 7.4 (3H, m, Ar), 4.7 – 4.5 (2H, m, CH), 3.6 – 3.5 (1H, m, CH_2), 3.4 – 3.2 (2H, m, CH, CH_2), 2.7 – 2.6 (1H, m, CH_2), 2.3 – 2.2 (1H, m, CH_2), 2.0 – 1.9 (2H, m, CH), 1.8 – 1.5 (4H, m, CH, CH_2), 1.5 – 1.3 (8H, m, CH, CH_2), 1.3 – 1.1 (4H, m, CH_2), 0.9 – 0.8 (18H, m, CH_3); δ_C (75.5 MHz; $CDCl_3$) 174.4, 174.3, 171.7, 171.6, 170.7, 166.1, 127.9, 125.8, 77.5, 77.08, 74.97, 74.77, 47.52, 47.39, 47.21, 42.78, 41.3, 34.6, 31.8, 31.8, 29.5, 26.7, 26.5, 23.9, 23.1, 22.5, 22.4, 21.5, 21.2, 16.9, 16.7, 16.4, 14.6, 11.9. Due to only a small amount of material available no further data was able to be collected.

4.4 ESTERIFICATION OF A NON-CONJUGATED CARBOXYLIC ACID IN THE PRESENCE OF A CONJUGATED ACID.

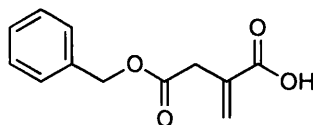
General Procedure



Itaconic acid (10 mmol), and NiCl₂·H₂O (2 mmol, 0.2 equiv.) were refluxed in alcohol (10 mL) for 48 hours. The reaction mixture was then cooled to room temperature and diluted with diethyl ether (20 mL). This was then washed with water and saturated sodium bicarbonate solution sequentially (3 x 10 mL). The aqueous extracts were combined and acidified to pH 1 with 1M HCl. The ester was extracted with diethyl ether (3 x 10 mL) and the combined extracts were concentrated *in vacuo*. The product could then be used without further purification.

2-((Methoxycarbonyl)methyl)acrylic acid (241)

Itaconic acid (1.30 g, 10 mmol) and methanol (10 mL) were reacted under the standard protocol to generate the desired compound as colourless crystalline needles (1.12 g, 78% yield); mp (hexane) 67°C; R_f (petrol:ethyl acetate, 4:1) 0.08; ν_{\max} (Nujol)/cm⁻¹ 2638 (COOH), 1728 (C=O), 1686 (COOH), 1632 (C=C), 1204 (C-O), 1168 (C-O); δ_H (300 MHz; CDCl₃) 11.78 (1H, s, OH), 6.41 (1H, s, C=CH), 5.78 (1H, s, C=CH), 3.64 (3H, s, CH₃), 3.28 (2H, s, CH₂); δ_C (75.5 MHz; CDCl₃) 171.9, 171.4, 133.5, 131.4, 52.6, 37.5; m/z (FAB⁺) 144 (99%, M⁺+H)[found 144.042908 M⁺+H C₁₇H₁₈O₄ requires M 144.042259]; Anal. Calc'd for C₁₇H₁₈O₄; C, 50.00; H, 5.59; N, 0.00. Found: C, 50.5; H, 5.69; N, 0.00.

2-(((Benzyloxy)carbonyl)methyl)acrylic acid (243)

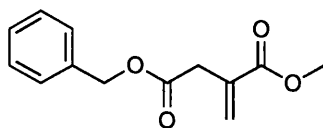
Itaconic acid (1.30 g, 10 mmol) and Benzyl alcohol (10 mL) were reacted under the standard protocol to generate the desired compound as colourless crystalline needles (1.52 g, 69% yield); mp (hexane) 95°C; R_f (petrol:ethyl acetate, 4:1) 0.12; ν_{\max} (Nujol)/ cm^{-1} 2725 (OH), 1723 (C=O), 1708 (COOH), 1623(C=C); δ_H (300 MHz; CDCl_3) 7.4 – 7.3 (5H, m, Ar), 6.59 (1H, s, C=CH), 5.85 (1H, s, C=CH), 5.17 (2H, s, CH_2), 3.41 (2H, s, CH_2); δ_C (75.5 MHz; CDCl_3) 171.3, 170.8, 136.1, 133.5, 131.4, 128.9, 128.7, 128.6, 67.2, 37.7; m/z (FAB+) 221 (99%, $\text{M}^+ + \text{H}$).

4.5 ESTERIFICATION OF CONJUGATED CARBOXYLIC ACIDS

General Procedure



To a solution of 1-(3-di-methylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (97.7 mg, 0.510 mmol), in dry DCM (10 mL) was added the acid (0.510 mmol) in dry DCM (5 mL), and the solution was stirred at room temperature for 30 minutes. To this mixture was added the alcohol in (0.255 mmol) in dry DMF and 4-(*N,N* dimethylamino)pyridine (DMAP) (10 mol%) and the mixture was stirred for a further 20 hours. The reaction was quenched with aqueous ammonium chloride and the product extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water (2 x 10 mL), brine (2 x 10 mL) and dried over magnesium sulphate. The residue was purified by flash column chromatography, hexane:ethyl acetate (3:1).

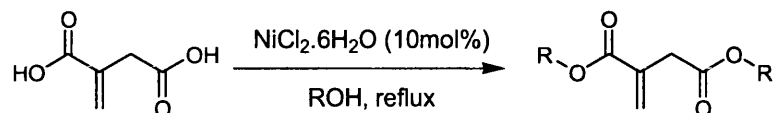
4-Benzyl 1-methyl 2-methylenesuccinate (244)

2-(((Benzyloxy)carbonyl)methyl)acrylic acid (0.22 g, 1 mmol) and methanol (10 mL) were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.047 g, 20% yield); R_f (petrol:ethyl acetate, 4:1) 0.3; δ_H (300 MHz; $CDCl_3$) 7.4 – 7.2 (5H, m, Ar), 6.31 (1H, d, J 1.2 Hz, C=CH), 5.66 (1H, d, J 1.2 Hz, C=CH), 5.13 (2H, s, CH_2), 3.57 (3H, s, CH_3), 3.28 (2H, d, J 1.1 Hz, CH_2); δ_C (75.5 MHz; $CDCl_3$) 171.5, 166.3, 136.17, 134.12, 129.3, 126.9, 128.6, 128.5, 67.2, 52.4, 37.9; Due to only a small amount of material being available no other data was collected.

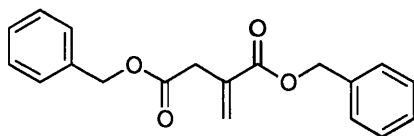
4.6 ESTERIFICATION OF BOTH THE CONJUGATED ESTER AND NON-CONJUGATED ESTER

General Procedure

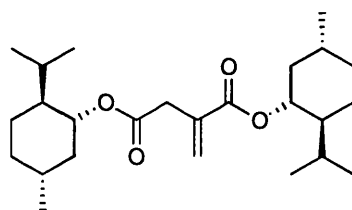
NiCl₂·6H₂O (10mol%)



Itaconic acid (10 mmol), and NiCl₂·H₂O (2 mmol, 0.2 equiv.) were refluxed in the alcohol (10mL) for 48 hours. The reaction mixture was then cooled to room temperature and diluted with diethyl ether (20 mL). This was washed with water and saturated sodium bicarbonate solution sequentially (3 x 10 mL). The organic extracts were then reduced *in vacuo*, and the residue purified by flash column chromatography (hexane:ethyl acetate, 6/1).

Dibenzyl 2-methylenesuccinate (245)

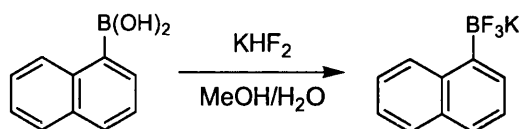
Itaconic acid (0.130 g, 1 mmol) and benzyl alcohol (10 mL) were reacted under the standard protocol to generate the desired compound as a colourless oil (0.049 g, 16% yield); R_f (petrol:ethyl acetate, 4:1) 0.2; ν_{\max} (Nujol)/ cm^{-1} 1739 (C=O), 1641 (C=C); δ_H (300 MHz; CDCl_3) 7.36 (10H, s, Ar), 6.42 (1H, s, C=CH), 5.75 (1H, s, C=CH), 5.20 (2H, s, PhCH_2), 5.13 (2H, s, PhCH_2), 3.44 (2H, s, CH_2); δ_C (75.5 MHz; CDCl_3) 170.9, 166.3, 136.1, 134.1, 129.4, 128.9, 128.8, 128.7, 128.6, 128.5, 67.2, 67.1, 38.2; Anal. Calc'd for $\text{C}_{19}\text{H}_{18}\text{O}_4$; C, 73.53; H, 5.85; N, 0.00. Found: C, 73.3; H, 5.85; N, 0.00.

Bis((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) 2-methylenesuccinate (246)

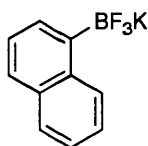
Itaconic acid (0.130 g, 1 mmol) and menthol (0.31 g, 2 mmol) in DCM (10 mL) were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.041 g, 10% yield); R_f (petrol:ethyl acetate, 4:1) 0.15; ν_{\max} (Nujol)/ cm^{-1} 1739 (C=O), 1641 (C=C), 1140 (C-O), 1081 (C-O); δ_H (300 MHz; CDCl_3) 6.22 (1H, s, C=CH), 5.58 (1H, s, C=CH), 4.6 – 4.5 (2H, m, CH), 3.4 – 3.2 (2H, m, CH_2), 2.0 – 1.8 (4H, m, CH), 1.8 – 1.6 (4H, m, CH, CH_2), 1.6 – 1.4 (6H, m, CH_2), 1.3 – 1.1 (4H, m, CH_2), 0.9 – 0.8 (18H, m, CH_3); δ_C (75.5 MHz; CDCl_3) 170.6, 166.0, 134.9, 128.1, 75.2, 75.0, 47.7, 41.1, 38.5, 34.9, 34.7, 34.6, 32.0, 31.8, 31.7, 26.7, 26.6, 26.2, 23.9, 23.8, 22.6, 22.4, 21.4, 21.1, 16.7.

4.7 SYNTHESIS OF POTASSIUM ORGANO TRIFLUOROBORATES FROM ORGANOBORONIC ACIDS

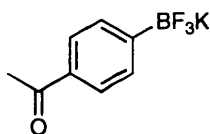
General Procedure



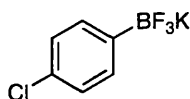
To a concentrated solution of the organoboronic acid (1.2 mmol) in methanol (3 mL) at room temperature, a saturated aqueous solution of potassium difluorohydride (4 mmol, 3.3 equiv) (caution: use Teflon vessel) was added dropwise. A heavy white precipitate was formed. Following the addition, the solvent was removed *in vacuo* at 40-50°C and the residual solid was thoroughly dried. It was then extracted with acetone (twice at room temperature and once with boiling solvent), the combined extracts were filtered and concentrated *in vacuo*. The product was used without further purification.

Potassium 1-naphthyltrifluoroborate (264)

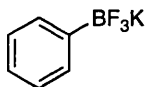
1-Naphthylboronic acid (0.206 g, 1.2 mmol) was reacted under the standard protocol to generate the desired compound as a colourless crystalline solid (0.19 g, 94% yield); mp (acetone) 100°C; R_f (petrol:ethyl acetate, 3:1) 0.11; ν_{\max} (Nujol)/cm⁻¹ 1630 (Ar); δ_H (300 MHz; ((CD₃)₂CO) 8.5 – 8.4 (1H, m, Ar), 7.6 – 7.5 (2H, m, Ar), 7.5 – 7.4 (1H, m, Ar), 7.2 – 7.1 (3H, m, Ar); δ_C (75.5 MHz; ((CD₃)₂CO) 132.1, 126.6, 126.5, 124.9, 124.4; δ_B (96 MHz; ((CD₃)₂CO) 4.9; Data identical to those in literature.¹⁰⁵

Potassium 4-acetylphenyltrifluoroborate (265)

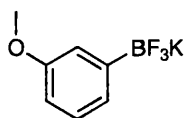
4-Acetylphenylboronic acid (0.196 g, 1.2 mmol) was reacted under the standard protocol to generate the desired compound as a pale yellow solid (0.22 g, 82% yield); mp (acetone) 302°C; R_f (petrol:ethyl acetate, 3:1) 0.06; ν_{\max} (Nujol)/cm⁻¹ 1758 (C=O), 1461 (Ar); δ_H (300 MHz; ((CD₃)₂CO) 7.72 (2H, d, J 7.7 Hz, Ar), 7.65 (2H, d, J 7.7 Hz, Ar), 2.49 (3H, s, CH₃); δ_C (75.5 MHz; ((CD₃)₂CO) 196.5, 134.6, 134.4, 133.8, 132.1, 127.3, 119.4, 28.4; δ_B (100 MHz; ((CD₃)₂CO) 4.1; Data identical to those in literature.¹⁰⁵

Potassium 4-chlorophenyltrifluoroborate (266)

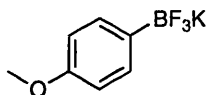
4-Chlorophenylboronic acid (0.187 g, 1.2 mmol) was reacted under the standard protocol to generate the desired compound as a colourless solid (0.21 g, 81% yield); mp (acetone) decomposed at 320°C; R_f (petrol:ethyl acetate, 3:1) 0.21; ν_{\max} (Nujol)/cm⁻¹ 1588 (Ar), 1458 (Ar), 721(CCl); δ_H (300 MHz; ((CD₃)₂CO) 7.45 (2H, d, J 8.0 Hz, Ar), 7.11(2H, d, J 7.6 Hz, Ar); δ_C (75.5 MHz; ((CD₃)₂CO) 134.6, 134.5, 131.8, 127.4; δ_B (100 MHz; ((CD₃)₂CO) 4.4; Data identical to those in literature.¹⁰⁵

Potassium phenyltrifluoroborate (267)

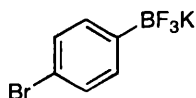
Phenylboronic acid (0.146 g, 1.2 mmol) was reacted under the standard protocol to generate the desired compound as colourless flakes (0.19 g, 90% yield); mp (acetone) decomposed at 310°C; R_f (petrol:ethyl acetate, 3:1) 0.08; ν_{\max} (Nujol)/cm⁻¹ 1490 (Ar); δ_H (300 MHz; (CD₃)₂CO) 7.5 – 7.3 (2H, m, Ar), 7.2 – 7.1 (3H, m, Ar); δ_C (75.5 MHz; (CD₃)₂CO) 132.9, 132.8, 127.4, 126.3; δ_B (MHz; ((CD₃)₂CO) 4.6; Data identical to those in literature.¹⁰⁵

Potassium 3-methoxyphenyltrifluoroborate (269)

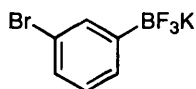
3-Methoxyphenylboronic acid (0.182 g, 1.2 mmol) was reacted under the standard protocol to generate the desired compound as a yellow solid (0.21 g, 83% yield); mp (acetone) 294°C; R_f (petrol:ethyl acetate, 3:1) 0.17; ν_{\max} (Nujol)/cm⁻¹ 2851 (OCH₃), 1576 (Ar); δ_H (300 MHz; ((CD₃)₂CO) 7.5 – 7.4 (1H, m, Ar), 6.7 – 6.6 (3H, m, Ar), 3.75 (3H, s, CH₃); δ_C (75.5 MHz; ((CD₃)₂CO) 129.8, 129.7, 128.7, 127.6, 126.8, 114.2, 55.9; δ_B (100 MHz; ((CD₃)₂CO) 4.3; Data identical to those in literature.¹²⁰

Potassium 4-methoxyphenyltrifluoroborate (270)

4-Methoxyphenylboronic acid (0.182 g, 1.2 mmol) was reacted under the standard protocol to generate the desired compound as yellow crystals (0.25 g, 96% yield); mp (acetone) decomposed at 273°C; R_f (petrol:ethyl acetate, 3:1) 0.2; ν_{\max} (Nujol)/cm⁻¹ 2853 (OCH₃); δ_H (300 MHz; ((CD₃)₂CO) 7.36 (2H, d, J 8.3 Hz, Ar), 6.68 (2H, d, J 8.0 Hz, Ar), 3.70 (3H, s, CH₃); δ_C (75.5 MHz; ((CD₃)₂CO) 133.8, 133.6, 132.4, 131.9, 119.6, 113.1, 55.4; δ_B (100 MHz; ((CD₃)₂CO) 4.7; Data identical to those in literature.¹⁰⁵

Potassium 4-bromophenyltrifluoroborate (272)

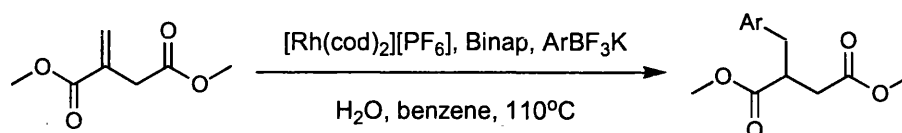
4-Bromophenylboronic acid (0.240 g, 1.2 mmol) was reacted under the standard protocol to generate the desired compound as pale yellow solid (0.27 g, 86% yield); mp (acetone) decomposed at 310°C; R_f (petrol:ethyl acetate, 3:1) 0.05; ν_{\max} (Nujol)/cm⁻¹ 1580 (Ar), 1462 (Ar), 740 (CBr); δ_H (300 MHz; ((CD₃)₂CO) 7.42 (2H, d, J 7.8 Hz, Ar), 7.27 (2H, d, J 8.1 Hz, Ar); δ_C (75.5 MHz; ((CD₃)₂CO) 135.1, 135.0, 130.6, 120.6; δ_B (100 MHz; ((CD₃)₂CO) 4.4; Data identical to those in literature.¹⁰⁰

Potassium 3-bromophenyltrifluoroborate (273)

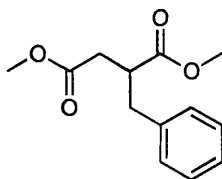
3-Bromophenylboronic acid (0.240 g, 1.2 mmol) was reacted under the standard protocol to generate the desired compound as a pale yellow solid (0.26 g, 82% yield); mp (acetone) 173-5°C; R_f (petrol:ethyl acetate, 3:1) 0.03; ν_{\max} (Nujol)/cm⁻¹ 1554 (Ar), 1460 (Ar), 733(C-Br); δ_H (300 MHz; ((CD₃)₂CO) 7.45 (1H, s, Ar), 7.28 (1H, d, J 7.1 Hz, Ar), 7.06 (1H, d, J 7.2 Hz, Ar), 6.91 (1H, t, J 7.5 Hz, Ar); δ_C (75 MHz; ((CD₃)₂CO) 135.6, 131.5, 130.9, 129.8, 129.2, 122.6; δ_B (100 MHz; ((CD₃)₂CO) 4.0; Data identical to those in literature.¹⁰⁰

4.8 RHODIUM CATALYSED ASYMMETRIC ADDITION OF POTASSIUM ORGANO(TRIFLUORO)BORATES TO DIMETHYL ITACONATE.

General Procedure

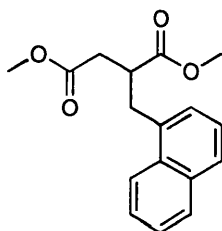


$[\text{Rh}(\text{COD})_2][\text{PF}_6]$ (0.004 g, 0.0075 mmol, 3 mol%) and (*R*)-BINAP (0.009 g, 0.0015 mmol) were added to a pressure tube. Degassed benzene (2 mL) was added after degassing and back filling with argon. After stirring briefly dimethyl itaconate (0.039 g, 0.25 mmol), potassium organotrifluoroborate (0.5 mmol, 2 equiv.) and water (0.1 mL) were added. The resulting solution was stirred at 110°C for 16 hours. The mixture was allowed to cool to room temperature, diluted with water (10 mL) and the product extracted with diethyl ether (3 x 15 mL). The combined extracts were washed with brine (3 x 10 mL), dried over magnesium sulphate and concentrated *in vacuo*. The crude product was then purified by flash chromatography (ethyl acetate:petrol, 1:4 by volume).

Dimethyl 2-benzylsuccinate (229)

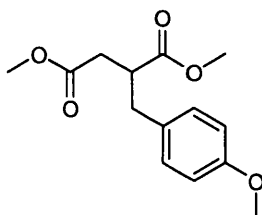
Dimethyl itaconate (0.039 g, 0.25 mmol), potassium trifluorophenylborate (0.092 g, 0.5 mmol), benzene (2 mL) and water (0.1 mL) were reacted under standard protocol to generate the desired compound as a pale yellow oil (0.03 g, 51% yield, 68% ee).

Diacel Chiralcel OD-H, hexane/propan-2-ol (95:5), 1.0 mL min⁻¹, t_R = 10.6 (*R*) and 12.4 (*S*).

Dimethyl 2-((naphthalen-1-yl)methyl)succinate (232)

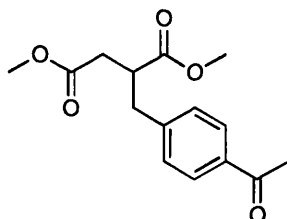
Dimethyl itaconate (0.039 g, 0.25 mmol), potassium trifluoro(1-naphthyl)borate (0.117 g, 0.5 mmol), benzene (2 mL) and water (0.1 mL) were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.04 g, 56% yield, 60% ee).

Diacel Chiralcel OD-H, hexane/propan-2-ol (95:5), 1.0 mL min⁻¹, t_R = 19.0 (*R*) and 28.9 (*S*).

Dimethyl 2-(4-methoxybenzyl)succinate (234)

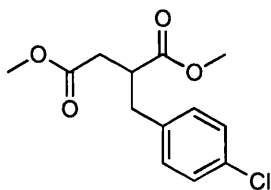
Dimethyl itaconate (0.039 g, 0.25 mmol), potassium trifluoro(4-methoxyphenyl)borate (0.107 g, 0.5 mmol), benzene (2 mL) and water (0.1 mL) were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.064 g, 93% yield, 62 % ee).

Diacel Chiralcel OD-H, hexane/propan-2-ol (95:5), 1.0 mL min⁻¹, *t_R* = 11.2 (*R*) and 16.5 (*S*).

Dimethyl 2-(4-acetylbenzyl)succinate (237)

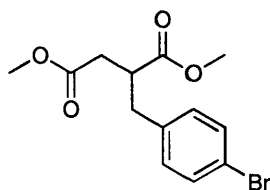
Dimethyl itaconate (0.039 g, 0.25 mmol), potassium trifluoro(4-acetylphenyl)borate (0.113 g, 0.5 mmol), benzene (2 mL) and water (0.1 mL) were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.066 g, 96% yield, 48% ee).

Diacel Chiralcel OD-H, hexane/propan-2-ol (95:5), 1.0 mL min⁻¹, *t_R* = 20.9 (*R*) and 33.4 (*S*).

Dimethyl 2-(4-chlorobenzyl)succinate (238)

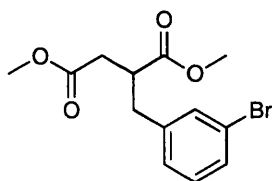
Dimethyl itaconate (0.039 g, 0.25 mmol), potassium trifluoro(4-chloro-phenyl)borate (0.109 g, 0.5 mmol), benzene (2 mL) and water (0.1 mL) were reacted under the standard protocol to generate the desired compound as a pale yellow solid (0.067 g, 96% yield, 60% ee).

Diacel Chiralcel OD-H, hexane/propan-2-ol (95:5), 1.0 mL min⁻¹, t_R = 7.7 (*R*) and 13.7 (*S*).

Dimethyl 2-(4-bromobenzyl)succinate (278)

Dimethyl itaconate (0.039 g, 0.25 mmol), potassium trifluoro(4-bromo-phenyl)borate (0.131 g, 0.5 mmol), benzene (2 mL) and water (0.1 mL) were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.077 g, 95% yield, 58% ee); R_f (petrol:ethyl acetate, 9:1) 0.18; ν_{\max} (Nujol)/ cm^{-1} 1742 (C=O), 1265 (C-O), 702 (CBr); δ_{H} (300 MHz; CDCl_3) 7.34 (2H, d, J 8.4 Hz, Ar), 6.96 (2H, d, J 8.4 Hz, Ar), 3.59 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 3.1 – 3.0 (1H, m, CH), 2.92 (1H, dd, J 6.6, 13.5 Hz, CH_2), 2.67 (1H, dd, J 7.8, 13.5 Hz, CH_2), 2.60 (1H, dd, J 8.7, 16.8 Hz, CH_2), 2.33 (1H, dd, J 5.2, 16.7 Hz, CH_2), δ_{C} (75.5 MHz; CDCl_3) 174.8, 172.5, 137.6, 132.1, 131.2, 121.1, 52.4, 52.3, 43.2, 37.5, 35.3; m/z (FAB+) 315 (20% M^+H) [315.024117 found M^+H $\text{C}_{13}\text{H}_{16}\text{O}_4^{79}\text{Br}_1$ requires M 315.023195;

Diacel Chiralcel OD-H, hexane/propan-2-ol (95:5), 1.0 mL min^{-1} , t_{R} = 8.0 (*R*) and 14.5 (*S*).

Dimethyl 2-(3-bromobenzyl)succinate (275)

Dimethyl itaconate (0.039 g, 0.25 mmol), potassium trifluoro(3-bromo-phenyl)borate (0.131 g, 0.5 mmol), benzene (2 mL) and water (0.1 mL) were reacted under the standard protocol to generate the desired compound as a pale yellow oil (0.075 g, 93% yield, 60% ee); R_f (petrol:ethyl acetate, 9:1) 0.2; ν_{\max} (Nujol)/ cm^{-1} 1742 (C=O), 1078 (C-O), 730 (CBr); δ_{H} (300 MHz; CDCl_3) 7.30 (1H, dt, J 1.5, 7.8 Hz, Ar), 7.25 (1H, s, Ar), 7.10 (1H, t, J 7.7 Hz, Ar), 7.02 (1H, d, J 7.5 Hz, Ar), 3.61 (3H, s, OCH_3), 3.59 (3H, s, OCH_3), 3.1 – 3.0 (1H, m, CH), 2.94 (1H, dd, J 6.6 Hz, 13.5, CH_2), 2.68 (1H, dd, J 8.1, 14.1 Hz, CH_2), 2.62 (1H, dd, J 8.5, 16.8 Hz, CH_2), 2.34 (1H, dd, J 5.1, 16.8 Hz, CH_2), δ_{C} (75.5 MHz; CDCl_3) 174.7, 172.5, 140.1, 132.4, 130.5, 130.3, 128.1, 122.6, 52.5, 52.3, 43.8, 37.7, 35.3; m/z (FAB+) 315 (20% $\text{M}^+ + \text{H}$) [315.024117 found $\text{M}^+ + \text{H}$ $\text{C}_{13}\text{H}_{16}\text{O}_4^{79}\text{Br}$ requires M 315.023195; Diacel Chiralcel OD-H, hexane/propan-2-ol (95:5), 1.0 mL min^{-1} , t_{R} = 19.0 (*R*) and 28.9 (*S*).

CHAPTER FIVE:
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CHAPTER SIX:
Appendices

6 APPENDICES

Rhodium catalysed addition of boronic acids to anhydrides: a new method for the synthesis of ketones

Christopher G. Frost* and Kelly J. Wadsworth

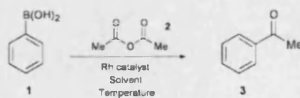
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The efficient transmetalation from boron to rhodium is exploited in a new synthesis of aryl and alkenyl ketones.

The rhodium catalysed addition of boronic acids to organic electrophiles has recently emerged as an important tool for organic synthesis.¹ An efficient transmetalation between boron and rhodium permits the addition of organoboronic acids to a range of activated olefins.² Significant advances have also been made in the coupling of unactivated olefins in aqueous media.³ Further to this the addition of aryl boronic acids to aldehydes and imines has been achieved.⁴ The mechanism of these transformations is proposed to involve transmetalation between the boronic acid and the rhodium(I) complex to afford an R–Rh(II) species. The nucleophilic R group then adds to the coordinated electrophile yielding either a Rh bound enolate or alkoxide which is subsequently hydrolysed. As part of our research programme developing catalysts for the functionalisation of aromatics, we were interested in the boron–rhodium transmetalation process as a means to promote the equivalent of a Friedel–Crafts acylation reaction of deactivated aryl derivatives. This is a demanding transformation which is not readily achieved by even the most effective Lewis acid catalysts.⁵ In this communication we wish to report our development of an efficient rhodium catalysed addition reaction that allows the synthesis of ketones from boronic acids under mild conditions.



Scheme 1 Rhodium catalysed acylation.

Table 1 Rhodium catalysed addition of 1 to acetic anhydride 2

Entry	Catalyst	Solvent (Temp./°C)	Yield of 3 (%)
1	—	Dioxane (100)	0
2	[Rh(acac)(ethylene)] ₂	Dioxane (100)	0
3	[Rh(acac)(ethylene)] ₂	DME–H ₂ O (65)	0 ^a
4	[Rh(acac)(cod)]	Dioxane (100)	16
5	[Rh(acac)(cod)]	DME–H ₂ O (65)	18 ^a
6	[Rh(acac)(nbd)]	Dioxane (100)	27
7	[Rh(acac)(nbd)]	DME–H ₂ O (65)	29 ^a
8	[Rh(nbd)Cl] ₂	Dioxane (100)	20
9	[Rh(cod)Cl] ₂	Dioxane (100)	57
10	[Rh(OAc) ₂]	Dioxane (100)	27
11	RhCl ₃ ·3H ₂ O	Dioxane (100)	0
12	[Rh(ethylene)Cl] ₂	Dioxane (100)	83
13	[Rh(ethylene)Cl] ₂	DME–H ₂ O (65)	84 ^a
14	[Rh(ethylene)Cl] ₂	Toluene (100)	17
15	[Rh(ethylene)Cl] ₂	THF (65)	37
16	[Rh(ethylene)Cl] ₂	DME (65)	85 ^a
17	[Rh(ethylene)Cl] ₂	DME (20)	76 ^a

^a DME–H₂O (6:1). ^b Yield after 2 hours. ^c Yield after 16 hours.

To demonstrate this concept, initial experiments examined the reaction of phenylboronic acid (1.6 equiv.) 1 with acetic anhydride 2 in the presence of 5 mol% of various rhodium complexes (Scheme 1).⁶ As summarised in Table 1, the formation of acetophenone 3 is symptomatic of an effective protocol for ketone synthesis.

The first point to note is that in the absence of catalyst no product formation is observed. It was interesting to learn that the Rh(acac) complexes favoured for addition to activated olefins, were not particularly effective in this case (entries 2–7). Similarly, the use of [Rh(OAc)₂]₂ and RhCl₃·3H₂O afforded disappointing results (entries 10 and 11). Gratifyingly, the use of [Rh(alkene)Cl]₂ complexes showed more promise (entry 9)

Table 2 Rhodium catalysed synthesis of ketones

Entry	Boronic acid	Product	Yield (%)
1			86
2			68
3			67
4			56
5			54
6			76
7			70
8			88
9			59
10			74

resulting in the formation of **3** in excellent overall yield in the best case (entry 12). The choice of solvent had a clear effect on the efficiency of the reaction (entries 12–16) with the reaction proceeding smoothly in dioxane and 1,2-dimethoxyethane (DME). The insensitivity of this protocol towards air and water (entry 13) is extremely beneficial from a practical perspective. At 65 °C in DME the reaction was complete within two hours, whilst at room temperature the reaction required 24 hours to afford comparable yields (entries 16 and 17). Furthermore, the catalyst loading could be lowered to 1.5 mol% with the product **3** being obtained in an 87% yield after 16 hours. Upon lowering to 0.1 mol% of catalyst, a modest 33% of **3** was isolated after the same period of time.

Under the optimised conditions the reaction was examined with respect to the scope of the boronic acid (Table 2).† An attractive feature of this methodology is the commercial availability of a wide range of boronic acids. An important point to note about the presented reaction is the regioselective formation of product with the electrophile substituting the boronic acid group. Therefore, whilst electronic effects (inductive and resonance) may influence the rates of the reactions, as a consequence of the nucleophilicity dictating the transmetalation and transfer processes, the composition of product is unaffected by the nature and position of substituent in the starting boronic acid. This offers a significant tactical advantage over Lewis acid catalysed electrophilic substitution processes. Thus, the reaction can be designed to mirror typical electrophilic substitution reactions (Table 2, entry 3). Conversely, the formation of *meta*- or *para*-substituted deactivated aromatics can be achieved in excellent isolated yield (Table 2, entries 1, 2 and 4). The results also confirm the scope of the reaction with the alternative electrophile, benzoic anhydride (Table 2, entries 6–10). Furthermore, the reaction can be extended to alkynylboronic acids with no significant loss in efficiency. At the present time, difficulties have been encountered in extending the methodology to acid chlorides.⁷ Further investigations are directed towards accomplishing this and the addition of organoboronic acids to other electrophiles.

In summary, a new rhodium catalysed addition of boronic acids has been developed that allows the synthesis of ketones.

This transformation proceeds in good yield for a range of boronic acids. Importantly, this new methodology offers specific advantages over traditional Lewis acid catalysed acylation reactions in that it allows the regioselective functionalisation of activated, unactivated and deactivated aromatics.

C. G. F. thanks Astra-Zeneca for a generous award from their strategic research fund.

Notes and references

† *General experimental procedure*: to a pressure tube charged with [Rh(ethylene)Cl]₂ (0.006 mmol, 1.5 mol%) was added 1,4-dioxane (4 ml), boronic acid (0.56 mmol) and anhydride (1 ml of 0.4 M solution). The tube was sealed, placed in a cold oil bath which was then heated to the required temperature and stirred for 16 hours. The mixture was allowed to cool to room temperature then worked up by extracting with ethyl acetate, washing with brine, drying over magnesium sulfate and concentrating *in vacuo*. The crude product was then purified by flash chromatography (ethyl acetate–hexane, 1:8 by volume). All the products have been satisfactorily characterised by ¹H NMR, ¹³C NMR and IR spectroscopy.

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Enantioselective rhodium-catalysed addition of boronic acids using C_2 -symmetric aryl diphosphite ligands

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Abstract

The enantioselective rhodium-catalysed conjugate addition of aryl boronic acids to dehydroalanine derivatives has been successfully carried out in the presence of C_2 -symmetric aryl diphosphite ligand (**R,R,R-4**) to prepare unnatural amino acid esters. The products have been obtained in up to 72% ee and with good isolated yield.

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Keywords: C–C coupling; Amino acids; Boronic acids; Rhodium; Conjugate addition

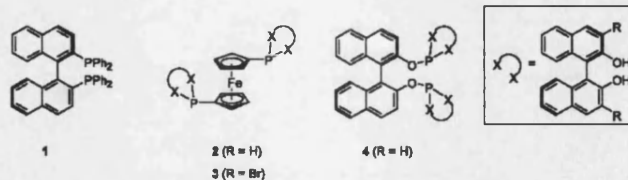
1. Introduction

The rhodium-catalysed addition of boronic acids to organic electrophiles has emerged as important methodology for organic synthesis. An efficient transmetalation between boron and rhodium permits the addition of organoboronic acids to a range of activated alkenes [1], aldehydes [2], imines [3] and anhydrides [4]. The use of the enantiopure diphosphine ligand BINAP (**R**)-**1** enables an enantioselective addition to cyclic enones and activated acyclic *E*-alkenes [5]. Recent work by Hayashi et al. [6] has elucidated the key steps in the catalytic cycle and revealed that $[\text{Rh}(\text{OH})(\text{BINAP})_2]$ complexes are the most effective pre-catalysts for the enantioselective addition. The reason for the improved activity is in part due to the high oxophilicity of boron resulting in an acceleration in the rate of transmetalation. Previously, α -substituted activated alkenes had not customarily been employed as substrates owing to their low reactivity. However, Hayashi et al. [7] have reported that 1-nitrocyclohexene is a satisfactory substrate in the enantioselective addition affording products with high enantioselectivity and good diastereoselectivity con-

trolled by protonation. In addition to this, work from our group has revealed a rhodium-catalysed conjugate addition of boronic acids to α,β -dehydroamino acid derivatives allowing rapid access to a wide range of substituted phenylalanine α -amino acids [8]. Li and coworker [9] first reported the analogous addition reaction using organotin and organobismuth reagents. The corresponding enantioselective reaction has been achieved by Reetz et al. [10] who reported one example of this type of transformation to prepare the naturally occurring amino acid phenylalanine. Importantly, Reetz noted that the BINAP-derived rhodium catalyst afforded excellent activity (100% conversion) but racemic product, whereas less-electron-rich diphosphonite ligands such as (**R,R**)-**2** afforded 37% ee increasing to 77% ee when 3,3'-dibromo-1,1'-binaphthyl-2,2'-diol-derived diphosphonite ligand (**R,R**)-**3** was used. In this case, enantioselectivity is influenced by facial selectivity and protonation. In this paper, we wish to present our studies on the enantioselective synthesis of amino acids by the addition of aryl boronic acids to dehydroalanine derivatives catalysed by a rhodium complex of an enantiopure diphosphite (**R,R,R**)-**4**. This ligand was first reported by Pringle and coworker [11] for nickel-catalysed hydrocyanations and has since been used in a variety of catalytic, enantioselective processes (Scheme 1).

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Scheme 1. Ligands for rhodium-catalysed addition of boronic acids.

2. Results and discussion

The ligands (*R,R,R*)-**4** and (*S,S,S*)-**4** were prepared in good yield by the literature methods [11]. Initial experiments examined the enantioselective addition of 1-naphthaleneboronic acid to α -phthalimidoacrylic ester (**5**) [12] and commercially available α -acetimidoacrylic ester (**7**); selected results are shown in Table 1. Disappointingly, there was no enantioselectivity using

substrate **5**, although in the case of the (*R*)-**1**-derived rhodium complex (entry 1), isolated yields of product **6** were excellent. To investigate whether the observed low enantioselectivity is a direct result of product racemisation under the reaction conditions, a sample of (*S*)-*L*-*N*-phthalimidophenylalanine ethyl ester (**6b**) was subjected to the reaction conditions. Analysis of the recovered amino acid derivative showed no change in enantioselectivity to that of the starting substrate (Scheme 2).

Table 1
Rhodium-catalysed synthesis of amino acid derivatives ^a

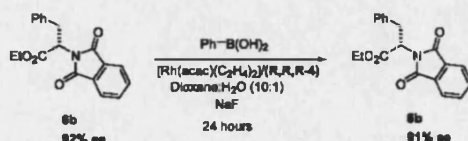
Entry	Enamide	Rh source	Ligand	Product	Yield (%) ^b	ee (%) ^c
1	5	[Rh(OH)(COD)] ₂	(<i>R</i>)- 1	6a	96	< 5
2	5	[Rh(OH)(COD)] ₂	(<i>R,R,R</i>)- 4	6a	6	< 5
3	5	[Rh(acac)(C ₆ H ₅) ₂]	(<i>R,R,R</i>)- 4	6a	40	< 5
4	7	[Rh(acac)(C ₆ H ₅) ₂]	(<i>R</i>)- 1	8a	81	< 5
5	7	[Rh(acac)(C ₆ H ₅) ₂]	(<i>R,R,R</i>)- 4	8a	91	72 (<i>S</i>)
6	7	[Rh(acac)(C ₆ H ₅) ₂]	(<i>S,S,S</i>)- 4	8a	86	71 (<i>R</i>)
7	7	[Rh(acac)(C ₆ H ₅) ₂]	(<i>R,R,R</i>)- 4	8a	71 ^d	71 (<i>S</i>)
8	7	[Rh(COE) ₂ Cl] ₂	(<i>R,R,R</i>)- 4	8a	98	70 (<i>S</i>)
9	7	[Rh(COD)Cl] ₂	(<i>R,R,R</i>)- 4	8a	98	50 (<i>S</i>)
10	7	[Rh(OH)(COD)] ₂	(<i>R,R,R</i>)- 4	8a	67	36 (<i>S</i>)
11	7	[Rh(acac)(C ₆ H ₅) ₂]		8a	2	
12	7	[Rh(COE) ₂ Cl] ₂		8a	3	
13	7	[Rh(COD)Cl] ₂		8a	43	
14	7	[Rh(OH)(COD)] ₂		8a	30	

^a General conditions: Rh (3 mol%), ligand (3.3 mol%), enamide (0.5 mmol), boronic acid (2 mmol), NaF (1.5 mmol), dioxane (1.5 ml), H₂O (150 μ l), 100 °C, 24 h.

^b Isolated yield after flash chromatography.

^c Determined by HPLC analysis using a chiral column (Chiralpak AD (10% 2-PrOH:hexane)).

^d 2.5 equivalents of boronic acid used with no NaF was added.



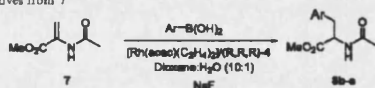
Scheme 2. Reaction conditions do not promote racemisation.





Better results in terms of enantioselectivity (up to 72% ee) were obtained when 7 was used as substrate (entries 5–9). It was noteworthy that the rhodium source had significant influence on enantioselectivity. Pertinent to this is the reactivity of the rhodium source in the absence of ligand (entries 11–14). The highest enantioselectivities result from the use of $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_5)_2]$ and $[\text{Rh}(\text{COE})_2\text{Cl}]_2$, both of which are ineffective without added ligand. NMR experiments indicate that ligand exchange ($(\text{R,R,R})\text{-4}(\text{C}_2\text{H}_5)_2$) is complete within 10 min at 25 °C, whereas exchange of COD is slower. The significant catalytic activity of $[\text{Rh}(\text{COD})\text{Cl}]_2$ and $[\text{Rh}(\text{OH})(\text{COD})]$ results in an increased proportion of racemic product thus lowering the overall enantioselectivity.

tivity. The enantioselectivities obtained under optimised conditions were repeatable and as would be expected, the use of the opposite enantiomer of ligand (S,S,S) **4** afforded a reversal in the sense of asymmetric induction (entry 6).

From the preceding results, the favoured pre-catalyst/ligand combination was revealed as $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]/(\text{R,R,R})\text{-4}$. Using the preferred conditions the scope of the process was explored with respect to the boronic acid (Table 2). In all cases, the reaction proceeded in good yield with modest but significant enantioselectivity. It was useful to note that both electron-rich and electron-deficient aryl boronic acids could be successfully employed using diphosphonic ligand $(\text{R,R,R})\text{-4}$. This

Table 2
Synthesis of amino acid derivatives from 7^a



Entry	Ar	Product	Yield [%] ^[a]	ee [%] ^[d]
1		8b	77	55 (S)
2		8c	79	48 (S)
3		8d	36	37 (S)
4		8e	73	56 (S)

^aGeneral conditions: Rh (3 mol%), ligand (3.3 mol%), enamide (0.5 mmol), boronic acid (2 mmol), NaF (1.5 mmol), dioxane (1.5 ml), H₂O (150 μ l), 100 °C, 24 h. ^bIsolated yield after flash chromatography. ^cDetermined by HPLC analysis using a chiral column (Chiralpak AD (10% 2-PrOH:hexane)).

is in contrast to $[\text{Rh}(\text{acac})(\text{R})-1]$ which is known to effect the hydrolysis of electron-rich arylboronic acids at 100 °C [6].

3. Conclusion

In summary, the use of enantiomerically pure diphosphite ligands has enabled the scope of the rhodium-catalysed addition of boronic acids to be extended to allow the preparation of enantiomerically enriched amino acids. The enantioselectivity is sensitive to the choice of rhodium pre-catalyst and key structural elements of the substrate. The prospect of tuning the ligand backbone to increase the facial selectivity of the dehydroalanine derivatives is currently being explored.

4. Experimental

Reactions were performed under a dry nitrogen atmosphere. Anhydrous dioxane was purchased from Sigma Aldrich and used as purchased, water was deoxygenated by sparging with nitrogen for 30 min and all other reagents were used without further purification. Melting points were determined using a Büchi 535 melting point apparatus and are uncorrected. Infrared spectra ($4000\text{--}600\text{ cm}^{-1}$) were recorded on a Perkin Elmer FT 1000 spectrometer with internal calibration. NMR spectra were recorded on a JEOL A-400 spectrometer or a Bruker DPX-300 spectrometer. Chemical shifts are reported in ppm, referenced to an internal SiMe_4 standard for ^1H - and ^{13}C -NMR. Mass spectra were recorded on a Finnigan MAT 8340 instrument at the University of Bath. Elemental analyses were performed with an Exeter analytical, Inc. CE-440 elemental analyser in the Chemistry Department at the University of Bath. High-performance liquid chromatography (HPLC) was performed on SP thermoSeparation products spectra SERIES system which uses chiral columns such as Chiralpak AD by Daicel Chemical Industry Ltd.

4.1. A typical procedure for the rhodium-catalysed 1,4 addition of boronic acids to dehydroalanine derivatives

An oven-dried Shlenk tube under nitrogen is charged with $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_5)_2]$ (3.9 mg, 15 μmol), ligand (16 μmol), enamide **5** or **7** (0.5 mmol), boronic acid (2 mmol), NaF (63 mg, 1.5 mmol) and dioxane (1.5 ml). The mixture was stirred at room temperature (r.t.) for 30 min and water (150 μl) added. The mixture was then stirred under an atmosphere of nitrogen at 100 °C for 24 h. After cooling to r.t. the solution was dissolved in ethyl acetate (3 ml) and water (5 ml) added. The aqueous layer was separated and extracted with ethyl acetate (3×5

ml), the combined organics were washed with brine (10 ml), dried (MgSO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography.

4.2. *N*-Phthalimido-3-(1-naphthyl)alanine ethyl ester (**6a**)

Colourless oil 96%; R_f (4:1, petrol:ethyl acetate) 0.38; m.p.: 87–90 °C; ν_{max} (Nujol) (cm^{-1}): 2924, 2852, 1773, 1744, 1711, 1597, 1462, 1386, 1276, 1251, 1199, 1103, 1028, 992, 945, 884, 798, 775, 720; ^1H -NMR (300 MHz, CDCl_3): δ 1.28 (3H, t, $J = 7.2$), 3.90 (1H, dd, $J = 11.3$, 14.7), 4.17 (1H, dd, $J = 4.5$, 14.7), 4.29 (2H, qd, $J = 1.1$, 7.2), 5.31 (1H, dd, $J = 4.5$, 11.3), 7.22–7.26 (2H, m), 7.43–7.51 (2H, m), 7.65–7.69 (3H, m), 7.72–7.76 (2H, m), 7.81 (1H, d, $J = 8.7$), 8.10 (1H, d, $J = 8.7$); ^{13}C -NMR (75.5 MHz, CDCl_3): δ 167.7, 166.2, 132.8, 132.6, 131.7, 130.5, 130.3, 127.7, 126.6, 126.0, 125.2, 124.5, 124.0, 122.2, 121.8, 60.9, 51.6, 30.6, 12.9; HRMS (FAB $^+$) [MH^+] Calc. for $\text{C}_{23}\text{H}_{20}\text{NO}_4$: m/z , 374.1392; Found: m/z , 374.1395. Anal. Calc. for $\text{C}_{23}\text{H}_{19}\text{NO}_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 73.6; H, 5.12; N, 3.75%.

4.3. *N*-Acetyl-3-(1-naphthyl)alanine methyl ester (**8a**)

Colourless solid 98%; R_f (petrol:ethyl acetate, 1:1) 0.20; m.p.: 90–91 °C; ^1H -NMR (300 MHz, CDCl_3): δ 1.91 (3H, s), 3.48 (1H, dd, $J = 6.6$, 14.1), 3.59 (1H, dd, $J = 6.3$, 14.1), 3.61 (3H, s), 5.01 (1H, m), 6.29 (1H, br d, $J = 7.9$), 7.22 (1H, app. d, $J = 6.8$), 7.36 (1H, app. d, $J = 8.3$), 7.45–7.56 (2H, m), 7.74 (1H, d, $J = 8.3$), 7.83 (1H, d, $J = 7.9$), 8.07 (1H, d, $J = 8.3$); ^{13}C -NMR (100.5 MHz, CDCl_3): δ 172.5, 170.0, 134.0, 132.6, 132.4, 129.0, 128.1, 127.5, 126.5, 126.0, 125.4, 123.7, 53.6, 52.6, 35.4, 23.4; ν_{max} (film) (cm^{-1}): 3430, 3310, 3017, 2954, 1741, 1669, 1512, 1437, 1374, 1215, 1130, 1022, 758, 668; HRMS (FAB $^+$) [MH^+] Calc. for $\text{C}_{16}\text{H}_{18}\text{NO}_3$: m/z , 272.1287; Found: m/z , 272.1275 (100%). Calc. for $\text{C}_{15}\text{H}_{17}\text{NO}_3$: m/z , 273.1320; Found: m/z , 273.1324 (18.1%). Anal. Calc. for $\text{C}_{16}\text{H}_{17}\text{NO}_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.2; H, 6.34; N, 5.04%.

4.4. *N*-Acetylphenylalanine methyl ester (**8b**)

Colourless oil 77%; R_f (petrol:ethyl acetate, 1:1) 0.22; m.p.: 66–68 °C; ^1H -NMR (300 MHz, CDCl_3): δ 1.98 (3H, s), 3.09 (1H, dd, $J = 5.7$, 13.8), 3.16 (1H, dd, $J = 6.0$, 13.8), 3.72 (3H, s), 4.88 (1H, m), 5.95 (1H, br d, $J = 6.4$), 7.07–7.10 (2H, m), 7.21–7.32 (3H, m); ^{13}C -NMR (75.5 MHz, CDCl_3): δ 172.5, 170.0, 136.2, 129.6, 129.0, 127.5, 53.5, 52.7, 38.2, 23.5; ν_{max} (film) (cm^{-1}): 3287, 3064, 3029, 2953, 2848, 1743, 1657, 1544, 1437, 1374, 1274, 1218, 1178, 1129, 1080, 1031, 1012, 985, 756, 701; FABMS: m/z , 222.1 (100%, MH^+). Anal. Calc. for

$C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.0; H, 6.93; N, 6.15%.

4.5. *N*-Acetyl-3-(4-biphenyl)alanine methyl ester (8c)

Pale solid 79%; R_f (petrol:ethyl acetate, 1:1) 0.18; m.p.: 152–154 °C; 1H -NMR (300 MHz, $CDCl_3$): δ 1.98 (3H, s), 3.11 (1H, dd, $J = 6.0, 13.9$), 3.19 (1H, dd, $J = 5.7, 13.9$), 3.72 (3H, s), 4.91 (1H, m), 6.25 (1H, br d, $J = 7.5$), 7.16 (2H, d, $J = 8.1$), 7.32 (1H, t, $J = 7.5$), 7.42 (2H, app. t, $J = 7.5$), 7.51 (2H, d, $J = 8.1$), 7.56 (2H, d, $J = 7.5$); ^{13}C -NMR (100.5 MHz, $CDCl_3$): δ 172.2, 169.9, 140.7, 140.1, 135.1, 129.8, 129.0, 127.5, 127.4, 127.1, 53.5, 52.7, 37.8, 23.5; ν_{max} (film) (cm^{-1}): 3348, 3029, 2954, 2358, 1752, 1653, 1533, 1488, 1437, 1375, 1217, 1172, 1129, 1007, 830, 761, 728, 695, 668; FABMS: m/z , 298.1 (100%, MH^+). Anal. Calc. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.6; H, 6.39; N, 4.66%.

4.6. *N*-Acetyl-3-(4-acetylphenyl)alanine methyl ester (8d)

Colourless solid 36%; R_f (petrol:ethyl acetate, 1:2) 0.17; m.p.: softens at 125 °C and melts at 144–146 °C; 1H -NMR (300 MHz, $CDCl_3$): δ 1.96 (3H, s), 2.55 (3H, s), 3.09 (1H, dd, $J = 6.0, 14.1$), 3.20 (1H, dd, $J = 6.0, 14.1$), 3.70 (3H, s), 4.88 (1H, dt, $J = 6.0, 7.8$), 6.18 (1H, br d, $J = 7.5$), 7.18 (2H, d, $J = 8.3$), 7.85 (2H, d, $J = 8.3$); ^{13}C -NMR (100.5 MHz, $CDCl_3$): δ 197.8, 171.9, 169.8, 141.8, 136.1, 129.7, 128.8, 53.3, 52.9, 38.3, 27.0, 23.5; ν_{max} (film) (cm^{-1}): 3286, 3076, 3016, 2959, 1746, 1678, 1608, 1549, 1216, 1183, 1126, 1017, 959, 832, 755, 666; FABMS: m/z , 264.1 (100%, MH^+). Anal. Calc. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.5; H, 6.48; N, 5.08%.

4.7. *N*-Acetyl-3-(4-methoxyphenyl)alanine methyl ester (8e)

Colourless solid 73%; R_f (petrol:ethyl acetate, 1:1) 0.18; m.p.: 94 °C; 1H -NMR (300 MHz, $CDCl_3$): δ 1.97 (3H, s), 3.00 (1H, dd, $J = 5.8, 13.8$), 3.07 (1H, dd, $J = 5.9, 13.8$), 3.71 (3H, s), 3.77 (3H, s), 4.82 (1H, m), 6.26 (1H, br d, $J = 7.8$), 6.82 (2H, d, $J = 8.7$), 7.01 (2H, d, $J = 8.7$); ^{13}C -NMR (100.5 MHz, $CDCl_3$): δ 172.3, 169.8, 158.7, 130.3, 127.9, 114.1, 55.5, 53.6, 52.6, 37.3, 23.5; ν_{max} (film) (cm^{-1}): 3431, 3019, 2955, 1743, 1675, 1612, 1513, 1438, 1374, 1250, 1216, 1178, 1128, 1035, 754, 669; FABMS: m/z , 252.1 (100%, MH^+). Anal. Calc. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.2; H, 6.76; N, 5.37%.

4.8. Chiral HPLC

The enantiomeric excess was determined by HPLC using either Daicel Chiralcel OD or Chiralpak AD Columns ($4.6 \times 250 mm^2$) at ambient temperature. The separation of mixtures under HPLC conditions is as follows: *N*-phthalimido-3-(1-naphthyl)alanine ethyl ester (6a) (AD, 1.0 ml min^{-1} , 10% 2-PrOH:hexane): (S) $t_1 = 13.7$ min, (R) $t_2 = 15.4$ min; *N*-acetyl-3-(1-naphthyl)alanine methyl ester (8a) (AD, 1.0 ml min^{-1} , 10% 2-PrOH:hexane): (R) $t_1 = 11.2$ min, (S) $t_2 = 14.1$ min; *N*-acetylphenylalanine methyl ester (8b) (AD, 1.0 ml min^{-1} , 10% 2-PrOH:hexane): (R) $t_1 = 10.2$ min, (S) $t_2 = 12.9$ min; *N*-acetyl-3-(4-biphenyl)alanine methyl ester (8c) (AD, 1.0 ml min^{-1} , 10% 2-PrOH:hexane): (R) $t_1 = 13.5$ min, (S) $t_2 = 21.5$ min; *N*-acetyl-3-(4-acetylphenyl)alanine methyl ester (8d) (AD, 1.0 ml min^{-1} , 10% 2-PrOH:hexane): (R) $t_1 = 32.2$ min, (S) $t_2 = 41.1$ min; *N*-acetyl-3-(4-methoxyphenyl)alanine methyl ester (8e) (OD, 1.0 ml min^{-1} , 10% 2-PrOH:hexane): (R) $t_1 = 13.9$ min, (S) $t_2 = 17.8$ min.

Configurations were established for *N*-acetyl-3-(1-naphthyl)alanine methyl ester (8a) and *N*-acetylphenylalanine methyl ester (8b) by chiral HPLC (Chiralcel OJ) and comparison to the literature values [13]. Other analogous products, which eluted in the same order by chiral HPLC (Chiralpak AD), were assigned the same absolute configuration. For example, (R,R,R)-4 produced *N*-acetylphenylalanine and substituted *N*-acetylphenylalanine derivatives which were eluted second by chiral HPLC (Chiralpak AD). All such products were assigned *S* absolute configuration. Configuration of *N*-phthalimido-3-(1-naphthyl)alanine ethyl ester was assigned by comparison of the HPLC (Chiralpak AD) elution times with those for a sample of *N*-phthalimido-3-phenylalanine ethyl ester produced from L-phenylalanine ethyl ester [14].

Acknowledgements

We are grateful to Johnson-Matthey for a CASE award to CJC and for the loan of transition metal salts. C.G.F. thanks Astra-Zeneca for a generous award from their strategic research fund.

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COMMUNICATION

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Rhodium catalysed tandem conjugate addition-protonation: an enantioselective synthesis of 2-substituted succinic esters†

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The rhodium catalysed addition of potassium trifluor(organoborates) to dimethyl itaconate generates an intermediate complex which on protonation provides enantioenriched succinic esters.

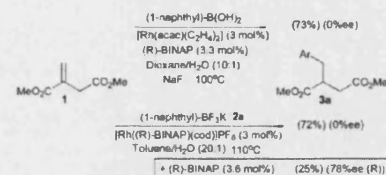
The rhodium catalysed asymmetric addition of aryl and alkenyl organoboron reagents to activated alkenes has emerged as fundamental methodology for organic synthesis.¹ The reaction can be carried out in aqueous solvent and affords excellent enantioselectivities (>90% ee) across a wide range of substrates. Interestingly, there are limited reports of α -substituted activated alkenes being employed as substrates.² This can be attributed to their lower reactivity and crucially, in the asymmetric process the enantioselectivity is determined at the hydrolysis step of an α - π -allylrhodium intermediate and not at the insertion step (Fig. 1).³

In previous reports, we and others, have revealed enantioselective rhodium catalysed additions of organoboranes to α,β -dehydroamino acid derivatives allowing access to a wide range of substituted phenylalanine α -amino acids ($Y = \text{NHAc}$, Fig. 1).⁴ In this paper we wish to present preliminary results in the first enantioselective synthesis of 2-substituted succinic esters by a tandem rhodium catalysed conjugate addition–enantioselective protonation.⁵

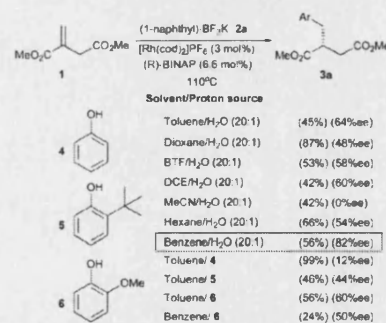
A preliminary investigation into the tandem 1,4-addition–enantioselective protonation by the addition of naphthyl or phenylboronic acid to dimethyl itaconate (**1**) in the presence of $\text{Rh}(\text{acac})(\text{C}_5\text{H}_5)_2$, (*R*)-BINAP and dioxane : water (10 : 1) as the solvent/proton source, afforded high yields of product **3a** (70–90%) but low enantioselectivity (<5% ee). In spite of prolonged attempts to optimise this process by changing or increasing the amount of ligand and other reaction parameters (solvent, temperature, rhodium complex), we were not successful in improving the enantioselectivity.⁶ It had been reported that potassium trifluor(organoborate) salts, which are easily prepared from the corresponding boronic acid, offer practical advantages in terms of reactivity and stability for rhodium catalysed conjugate addition reactions.⁷ Our initial experiments confirmed that the addition of **2a** to **1** was promoted by complexes formed from cationic rhodium salts, with complexes formed from neutral species such as

$\text{Rh}(\text{acac})(\text{C}_5\text{H}_5)_2$ failing to efficiently catalyse the reaction. Interestingly, we noted that additional chiral ligand was essential to achieve good asymmetric induction with either pre-formed complexes or those prepared *in situ* (Scheme 1).⁸ It is feasible that the pre-formed rhodium–BINAP complex decomposes to an active but achiral catalyst in the absence of extra ligand, however this does not occur with simpler substrates under similar conditions. The excess ligand could effect the enantioselective protonation by blocking free coordination sites on rhodium or possibly suppressing facial isomerisation of the α - π -allyl intermediate.⁹ Further studies are under way to determine the composition of the enantioselective catalyst.

The enantioselectivity proved to be highly dependent on the solvent system (Scheme 2). For convenience we performed the addition of trifluor(organoborate) salts to dimethyl itaconate (**1**) in the presence of a cationic rhodium complex prepared *in situ* from $[\text{Rh}(\text{cod})_2][\text{PF}_6]$ and (*R*)-BINAP in a solvent–water mix (20 : 1) at 110 °C as described by Davies and Genêt for the addition to 2-cyclohexenone but with additional ligand (2.2 equiv.).¹⁰ It is useful to note that the use of benzene as solvent resulted in a significant enhancement of enantioselectivity compared to toluene and dioxane, the usual solvents of choice for enantioselective rhodium catalysed conjugate additions. The nature of the proton source is known to be important when enantioselectivity is



Scheme 1 Additional ligand required for enantioselectivity.



Scheme 2 The effect of changing solvent and proton source.

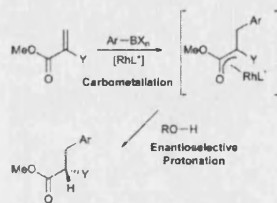


Fig. 1 Enantioselectivity controlled by protonation.

† Electronic supplementary information (ESI) available: experimental procedures and HPLC data. See <http://www.rsc.org/suppdata/cc/b4/b406905f>

Table 1 Scope of rhodium catalysed conjugate addition-protonation

R-BINAP-K	Ligand	Yield (%) ^a	Ec (%) ^b
	(R)-BINAP	51	68 (R)
	(R)-BINAP	Trace	N.d.
	(R)-BINAP (S)-BINAP	51 ^c 82 ^d	64 (R) 64 (S)
	(R)-BINAP (S)-BINAP	89 93	62 (R) 56 (S)
	(R)-BINAP (S)-BINAP	75 96	48 (R) 46 (S)
	(R)-BINAP (S)-BINAP	80 93	60 (R) 54 (S)
	(R)-BINAP (S)-BINAP	85 95	58 (R) 62 (S)
	(R)-BINAP (S)-BINAP	89 96	60 (R) 60 (S)
	(S)-BINAP	80 ^e	46 (S)

^a Isolated yield after column chromatography. ^b The absolute configuration of the products were assigned by comparison of the retention time of previously assigned enantiomers using chiral HPLC (Chiracel (DH-10, hexane/isopropanol 95:5)). ^c Isolated with 10% of 3,4-isomer. ^d Isolated with 32% of 3,4-isomer. ^e Isolated with 33% of 3,4-isomer.

dependent on a face selective protonation of the intermediate oxo- π -allylrhodium species.⁴ In this process, the application of sterically-hindered phenols as alternative proton sources revealed a significant correlation between structure and enantioselectivity.¹¹ However, the system could not be optimized to surpass the reproducible selectivity obtained using water.

The practical utility of the methodology was demonstrated by the addition of a diverse range of trifluoroborate salts (2b-j) (Table 1, ESI†). With the exception of *ortho*-substituted 2c, the products were isolated in excellent yield and reproducible enantioselectivity. In the presence of (R)-BINAP the product with (R) configuration was obtained, consistent with *S*/face protonation of the oxo- π -allylrhodium intermediate. Of particular note is the alkenylation process (addition of 2d and 2j) which provides products that could not ordinarily be obtained by approaches involving enantioselective hydrogenation.

Finally, it should be pointed out that high temperature (>100 °C) is essential for enantioselectivity. Attempts to lower the reaction temperature resulted in racemic mixtures of product (3a-j).¹² The multifarious factors that control asymmetric induction in the addition to α -substituted activated alkenes are the subject of continued study and will be reported in due course.

The authors would like to thank Johnson-Matthey for the generous loan of transition-metal salts and Professor Richard Jackson (University of Sheffield) for discussion and insightful comments related to the presented work.

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- A range of 2,6-disubstituted phenols were also tested resulting in modest enantioselectivities (20–45%).
- High yields of racemic product 3a are obtained at 60 °C and 80 °C with either pre-formed complexes or those prepared *in situ*.

2022

LETTER

Rhodium-Catalysed 1,4-Additions in Water: Synthesis of Succinic Esters and β^2 -Amino Acid Derivatives

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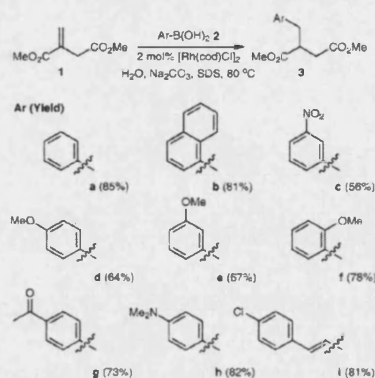
Abstract: The rhodium-catalysed addition of boronic acids to α -substituted activated alkenes proceeds smoothly in water resulting in a unique synthesis of both succinic esters and β^2 -amino acid derivatives.

Key words: conjugate addition, rhodium, boronic acids, succinic esters, β^2 -amino acids

Since the first report by Hayashi and Miyaura in 1998, the rhodium-catalysed addition of aryl and alkenyl organometallic reagents to activated alkenes has emerged as an important methodology for organic synthesis.¹ Although both Miyaura and Lautens have reported additions to both activated alkenes and heteroaromatic alkenes that proceed with water as solvent, in the majority of reported examples organic solvents are used either alone or as co-solvents.² In a previous study we have revealed an efficient rhodium-catalysed conjugate addition of boronic acids to α,β -dehydroamino acid derivatives using water as the only solvent.³ In an ongoing programme of research we have sought to broaden the scope of this methodology to other α -substituted activated alkenes. In this paper, we wish to present preliminary results in the synthesis of 2-substituted succinic esters and β^2 -amino acid derivatives. The products from this process are of significant utility as peptidomimetics in the development of pharmaceutical and agrochemical intermediates.⁴ The methodology described herein represents a unique alternative to the two-step condensation-hydrogenation approach conventionally employed.⁵

At the outset of this study we chose to investigate the coupling of arylboronic acid (**2h**) with dimethyl itaconate (**1**) using water as the reaction solvent. During preliminary optimisation, the catalyst $[\text{Rh}(\text{cod})\text{Cl}]_2$ (cod = cycloocta-1,5-diene) was used with sodium dodecylsulfate (SDS) as a phase transfer agent affording a 55% yield of product **3b**. In the absence of SDS the yield fell to less than 10%. The addition of two equivalents of sodium carbonate increased the yield to 81%. Under these optimised conditions a number substituted of substituted aryl and vinylboronic acids (**2a–i**) was tested and, pleasingly the reaction proceeded in good isolated yield to provide a useful synthetic approach to 2-substituted succinic esters

(Scheme 1).⁶ The addition of phosphine ligands did not appear to accelerate the conjugate addition under these conditions. It was useful to note that both electron-rich (**3h**) and electron-deficient aryl boronic acids (**3c,g**) could be successfully employed as well as different substitution patterns (**3d–f**). The incorporation of functional groups such as -Cl, -COMe, -NO₂ and -NMe₂ provide pharmacologically interesting products and present opportunities for further modification.



Scheme 1

Given the importance of β -amino acids and their derivatives the development of new synthetic methodology to prepare such compounds is of significant interest.⁷ We were therefore driven to extend the described methodology to include the addition of boronic acids to β -amidoacrylates affording β^2 -amino acid derivatives. The orthogonally protected β -amidoacrylate substrate **4** can be prepared in good yield by the reaction of potassium phthalimide (KNPht) with either of bromomethylacrylate or acetoxymethylacrylate.^{7b,c} We were pleased to discover that this was a viable route for the synthesis of functionalised β^2 -phenylalanine derivatives. As previously the combination of $[\text{Rh}(\text{cod})\text{Cl}]_2$ and sodium dodecylsulfate (SDS) provided a catalyst system for the addition of a range of substituted boronic acids in water (Scheme 2).⁹ The lower reactivity of **4** is evident from the higher

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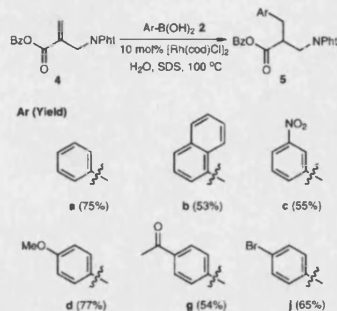
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LETTER

Synthesis of Succinic Esters and β^2 -Amino Acid Derivatives

2023

catalyst loading (10 mol%) and higher temperature (100 °C) necessary to afford acceptable isolated yields of product (53–77%). Nevertheless, this represents a new practical method for the synthesis of highly functionalised β^2 -amino acid derivatives and we are continuing to expand the scope of the transformation. The protecting groups can be cleaved by a two-step route consisting of hydrogenolysis of the benzyl group followed by removal of the phthalyl group with hydrazine.^{7b} Alternatively, the simultaneous cleavage of both protecting groups can occur under acidic conditions (6 N HCl–HOAc 4:1) affording the β^2 -amino acid hydrochloride salts.^{3,10}



Scheme 2

The key steps in the catalytic cycle have been elucidated and reported by Hayashi.¹¹ Assuming the mechanistic observations extend to the presented work, it is likely a rhodium-hydroxide species is the reactive catalyst and the reaction occurs by aryl transfer to rhodium followed by coordination of the substrate (1/4) and insertion to generate an α - π -allyl rhodium species which is hydrolysed to provide the final product (3/5). The methodology presented here provides a practical route to racemic 2-substituted succinic esters and β^2 -amino acid derivatives using water as the solvent. We are currently investigating a rhodium-catalysed enantioselective conjugate addition to substrates 1 and 4 employing organoboron reagents and we will report these results in due course.¹²

Typical Experimental Procedure: Dimethyl itaconate (1, 0.210 g, 1.308 mmol), 1-naphthylboronic acid (2b, 0.578 g, 3.36 mmol, 2.5 equiv), SDS (0.189 g, 0.684 mmol, 0.5 equiv) and Na_2CO_3 (0.291 g, 3.648 mmol, 2.0 equiv) were added to a solution of $[\text{Rh}(\text{cod})\text{Cl}]_2$ (0.012 g, 0.058 mmol, 2 mol%) in water (6.6 mL). The resulting solution was stirred at 80 °C overnight. After cooling to r.t. the product was extracted with Et_2O (3 \times). The organic extracts were then combined, washed with brine (3 \times) and dried with MgSO_4 . Flash chromatography in (4:1) petroleum ether–EtOAc afforded the product 3b as a colourless crystalline solid (65%). Mp 96–97 °C (lit.¹³ 96.7 °C). ^1H NMR (300 MHz, CDCl_3): δ = 2.37 (1 H, dd, J = 5.1, 17.1 Hz, CH_2), 2.69 (1 H, dd, J = 9.3, 17.1 Hz, CH_2), 3.06 (1 H, dd, J = 9.3, 13.5 Hz, CH_2), 3.25 (1 H, m, CH_2), 3.52 (2 H, dd, J = 5.7,

13.5 Hz, CH_2), 3.54 (3 H, s, CH_3), 3.61 (3 H, s, CH_3), 7.21 (1 H, d, J = 8.1 Hz, Ar), 7.32 (1 H, t, J = 6.9 Hz, Ar), 7.46 (2 H, m, Ar), 7.69 (1 H, d, J = 8.4, Ar), 7.80 (1 H, d, J = 9.3, Ar), 8.02 (1 H, d, J = 8.7, Ar). ^{13}C NMR (75.5 MHz, CDCl_3): δ = 35.5, 35.6, 42.5, 52.1, 52.4, 123.9, 125.7, 126.1, 126.7, 127.8, 128.1, 129.3, 132.1, 134.3, 134.6, 175.3, 172.6. IR (nujol): 1159 (s), 1377 (s), 1462 (s), 1719 (m), 2724 (m), 2862 (br cm^{-1}). MS (FAB $^+$): m/z (%) = 286 (56) $[\text{M}^+ + \text{H}]$. HRMS (FAB $^+$): $\text{C}_{17}\text{H}_{16}\text{O}_4$ requires $[\text{M}]$: 286.1205; found: 286.1210 $[\text{M}^+ + \text{H}]$. Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{O}_4$: C, 71.31; H, 6.34. Found: C, 71.30; H, 6.34%.

Acknowledgment

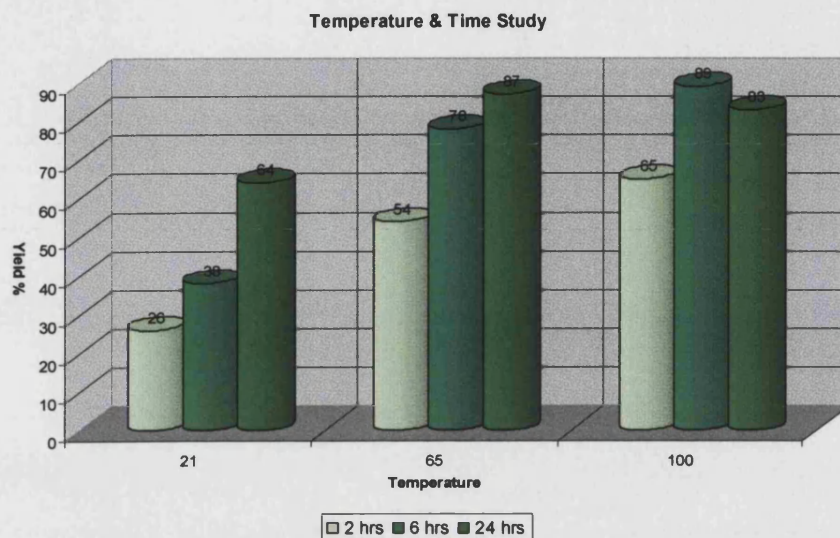
We are grateful to Johnson-Matthey for the loan of transition metal salts and a CASE award to CJC. CGF thanks Pfizer for further generous support.

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- (3 H, s), 3.59 (3 H, s), 3.75 (3 H, s), 6.79 (2 H, m), 7.00 (1 H, d, $J = 9.0$ Hz), 7.15 (2 H, m). Compound 3g: ^1H NMR (300 MHz, CDCl_3): $\delta = 2.35$ (1 H, dd, $J = 5.1, 16.8$ Hz), 2.63 (2 H, dd, $J = 8.4, 16.8$ Hz), 2.78 (2 H, dd, $J = 7.5, 12.9$ Hz), 3.07 (2 H, m), 3.58 (3 H, s), 3.59 (3 H, s), 7.19 (2 H, d, $J = 8.4$ Hz), 7.83 (2 H, d, $J = 8.1$ Hz). Compound 3h: ^1H NMR (300 MHz, CDCl_3): $\delta = 2.33$ (1 H, dd, $J = 4.8, 16.8$ Hz), 2.58 (2 H, m), 2.85 (6 H, s), 2.99 (2 H, m), 3.56 (3 H, s), 3.61 (3 H, s), 6.60 (2 H, d, $J = 8.7$ Hz), 6.95 (2 H, d, $J = 8.7$ Hz). Compound 3i: ^1H NMR (300 MHz, CDCl_3): $\delta = 2.32$ (3 H, m), 2.64 (1 H, dd, $J = 8.7, 16.5$ Hz), 2.91 (1 H, m), 3.58 (3 H, s), 3.63 (3 H, s), 6.00 (1 H, m), 6.30 (1 H, d, $J = 15.6$ Hz), 7.19 (4 H, s).
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- (9) All compounds have been satisfactorily characterised by ^1H NMR and ^{13}C NMR. ^1H NMR data (300 MHz, CDCl_3) for 5a: $\delta = 2.85$ (1 H, dd, $J = 6.6, 14.1$ Hz), 3.10 (1 H, dd, $J = 8.7, 14.1$ Hz), 3.35 (1 H, m), 3.85 (1 H, dd, $J = 6.0, 13.8$ Hz), 4.05 (1 H, dd, $J = 8.4, 13.8$ Hz), 5.00 (2 H, s), 7.10–7.25 (10 H, m), 7.67 (2 H, m), 7.78 (2 H, m). Compound 5b: ^1H NMR (300 MHz, CDCl_3): $\delta = 3.36$ (1 H, m), 3.50 (2 H, m), 3.95 (1 H, dd, $J = 4.8, 13.8$ Hz), 4.15 (1 H, dd, $J = 7.8, 13.8$ Hz), 4.95 (2 H, s), 7.05 (2 H, dd, $J = 1.7, 7.7$ Hz), 7.15 (2 H, m), 7.30 (3 H, m), 7.45 (2 H, m), 7.60–7.88 (6 H, m), 8.00 (1 H, d, $J = 8.4$ Hz). Compound 5c: ^1H NMR (300 MHz, CDCl_3): $\delta = 3.00$ (1 H, dd, $J = 5.9, 14.0$ Hz), 3.15 (1 H, dd, $J = 9.2, 14.0$ Hz), 3.35 (1 H, m), 3.90 (1 H, dd, $J = 6.0, 13.8$ Hz), 4.08 (1 H, dd, $J = 7.8, 13.8$ Hz), 5.00 (2 H, s), 7.15 (2 H, m), 7.25 (3 H, m), 7.35 (1 H, m), 7.50 (1 H, d, $J = 7.8$ Hz), 7.70 (2 H, m), 7.85 (2 H, m), 8.00 (1 H, d, $J = 8.1$ Hz), 8.05 (1 H, s). Compound 5d: ^1H NMR (300 MHz, CDCl_3): $\delta = 2.80$ (1 H, dd, $J = 6.6, 13.8$ Hz), 3.00 (1 H, dd, $J = 8.6, 14.0$ Hz), 3.30 (1 H, m), 3.75 (3 H, s), 3.85 (1 H, dd, $J = 6.0, 13.8$ Hz), 4.05 (1 H, dd, $J = 8.3, 13.7$ Hz), 5.00 (2 H, s), 6.75 (2 H, d, $J = 8.7$ Hz), 7.05 (2 H, d, $J = 8.7$ Hz), 7.15 (2 H, m), 7.23 (3 H, m), 7.68 (2 H, m), 7.78 (2 H, m). Compound 5g: ^1H NMR (300 MHz, CDCl_3): $\delta = 2.55$ (3 H, s), 2.95 (1 H, dd, $J = 6.3, 14.1$ Hz), 3.15 (1 H, dd, $J = 8.7, 14.1$ Hz), 3.35 (1 H, m), 3.90 (1 H, dd, $J = 6.2, 14.0$ Hz), 4.05 (1 H, dd, $J = 8.1, 13.8$ Hz), 5.00 (2 H, s), 7.15 (2 H, m), 7.18–7.28 (5 H, m), 7.70 (2 H, m), 7.78 (4 H, m). Compound 5j: ^1H NMR (300 MHz, CDCl_3): $\delta = 2.80$ (1 H, dd, $J = 6.5, 14.0$ Hz), 3.00 (1 H, dd, $J = 9.0, 14.1$ Hz), 3.30 (1 H, m), 3.90 (1 H, dd, $J = 6.3, 13.8$ Hz), 4.05 (1 H, dd, $J = 8.1, 13.8$ Hz), 5.00 (2 H, s), 7.05 (2 H, d, $J = 8.4$ Hz), 7.15 (2 H, m), 7.23 (3 H, m), 7.29 (2 H, d, $J = 8.4$ Hz), 7.70 (2 H, m), 7.80 (2 H, m).
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performed at 100°C where a *reduction* of yield between 6 hours and 24 hours is observed (Graph 1).



Graph 1

Catalyst Loading Study

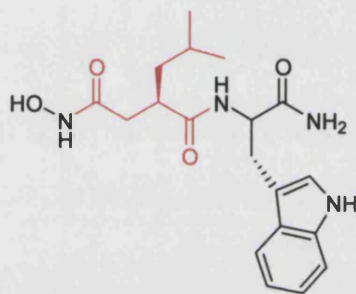
The study of the optimal catalyst loading proved once again that there is a fine balance in this reaction between the acceleration of the desired reaction and the production of unwanted side products. Although none of these side products were isolated they are likely to include benzene through hydrolysis of the boronic acid.

It is pleasing to note that a 33% yield can be achieved with catalyst loadings of as low as 0.1mol%. However, there is a decrease of 15% yield when the loading is increased from 3mol% to 5mol%. Thus, 3mol% is the optimum catalyst loading for a 16 hour reaction at 65 °C (Table 6).

3 RHODIUM-CATALYSED ADDITIONS TO ITACONATE ESTERS

3.1 AIMS AND OBJECTIVES

The object of this project was to explore the 1,4-addition of organoboronic acids to dialkyl itaconate esters, the products of which are synthetically useful as they are important intermediates for the synthesis of many natural products; for example, matrix metalloproteinase inhibitor **199**.⁸²



199

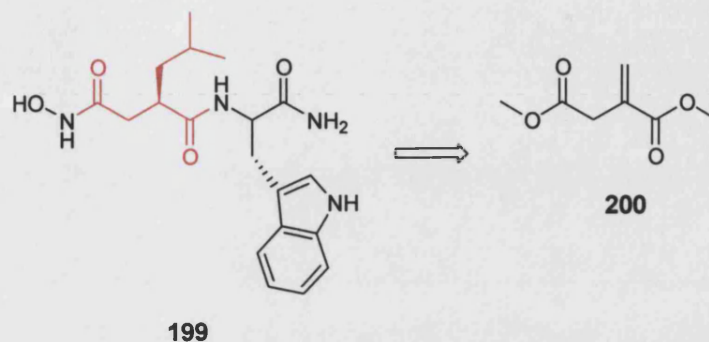
Figure 1

Initial studies will focus on the racemic synthesis of 2-substituted succinic esters, through the study of a range of rhodium complexes and conditions. It was felt that aqueous conditions would be optimum for environmental reasons as well as suitability towards a range of functional groups. Once optimal conditions have been established, a series of 2-substituted succinic esters will be prepared from a range of boronic acids and a select group of dialkyl itaconate esters.

Once a route to racemic products has been identified, focus will be switched to developing an asymmetric version of this reaction. This will entail an investigation of key reaction parameters including a variety of rhodium salts, enantiopure ligands, organoboranes and additives. After a thorough optimisation a range of 2-substituted succinic esters will be prepared in both (*R*)- and (*S*)-configurations.

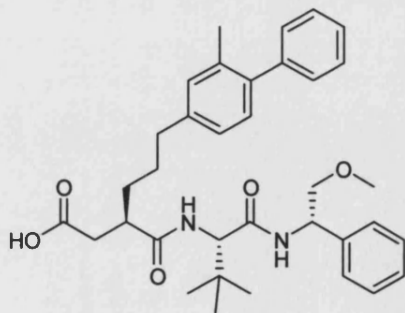
3.2 BACKGROUND

The synthetic usefulness of 2-substituted succinic esters can be demonstrated by looking at the synthesis of three major drugs, MMP inhibitors, lignan lactones and CNS drugs.



Scheme 76

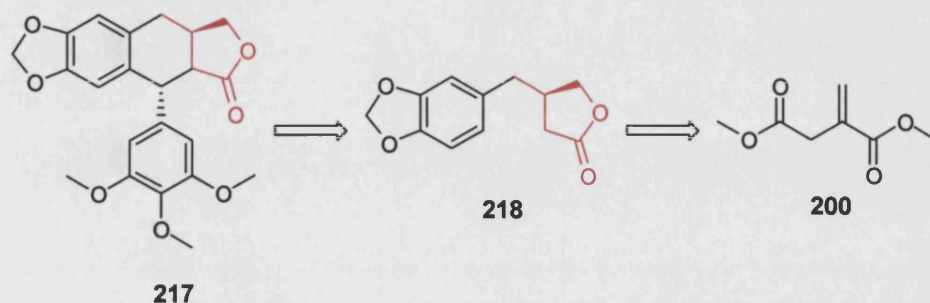
Matrix metalloproteinases (MMP's) are a group of enzymes involved in the repair, degradation, and remodelling of extracellular matrix proteins in tissues. Since they have a destructive potential, failure to regulate MMP activity in physiological processes may lead to such problems as tissue destruction, and diabetic ulcers.⁸² UK-370, 106, **201**, a potent and selective MMP-3 inhibitor discovered by chemists at Pfizer,⁸³ has been developed as a candidate to treat pathological conditions, involving tissue destruction.



UK-370, 106 **201**

Figure 2

Lignan lactones such as deoxypodophyllotoxin **217** are known to show cytotoxic activities and can be utilised as anti-cancer drugs. Achiwa *et al.*⁸⁷ synthesised a range of these compounds using the asymmetric form of the above route. A retrosynthesis of which is shown in Scheme 81.

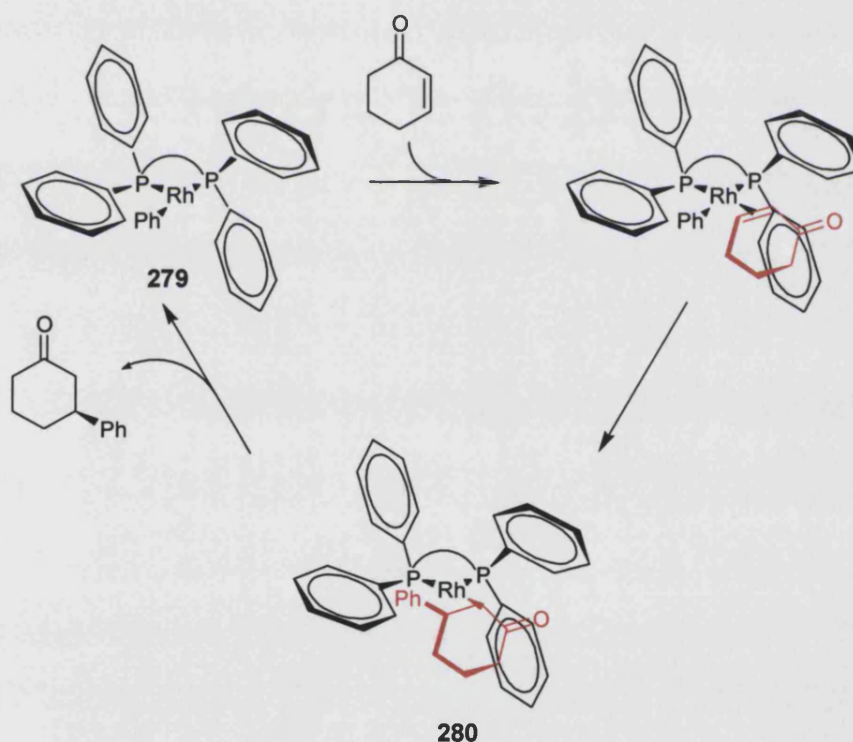


Scheme 81

Stobbe condensation of dimethyl itaconate and the required substituted benzaldehyde was followed by asymmetric hydrogenation of the alkene (Scheme 82). The asymmetric hydrogenation was carried out in methanol at 30°C for 40 hours under 1 atm. of H₂ in the presence of triethylamine using the neutral rhodium complex of (4*S*,5*S*)-MOD-DIOP **220**. This is prepared by mixing [Rh(COD)Cl]₂ and MOD-DIOP in methanol. All reactions gave high optical purity (>93%ee) and quantitative yields. Optically pure (*R*)-arylmethylsuccinic acid monomethyl esters **219** were easily obtained by a single recrystallisation of the products from isopropyl ether.

mechanism demonstrates how the ligand determines which face the alkene coordinates (Scheme 100).

BINAP has been extensively studied and so the skewed structure of **279** is known to reflect its interaction with transition metals. It can be seen that (*S*)-BINAP rhodium intermediate **279** has a free space in the lower part of the coordination site. The upper part being blocked by one of the phenyl rings of the BINAP ligand. This forces the alkene of cyclohexenone to coordinate through its α -si face rather than its α -re face. Migratory insertion then creates a stereocentre in **280** with absolute configuration (*S*). This model can be used to predict a host of 1,4-addition products configuration with the (*S*)-BINAP rhodium intermediate always attacking the α -si face of the α,β -unsaturated carbonyl.



Scheme 100

The situation is complicated further when the protonolysis occurs to form a new chiral centre. For example Hayashi reported that organoboronic acids react with α -